Study for assessing prevalence and phenotype

Of Local allergic rhinitis

Thesis

Submitted for partial fulfillment of master degree in internal medicine

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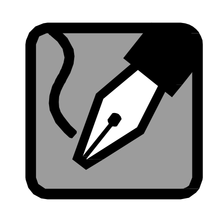
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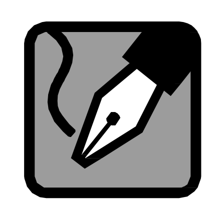
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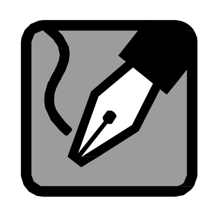
Introduction and Aim of the work





Review of Literature





Subjects and Methods





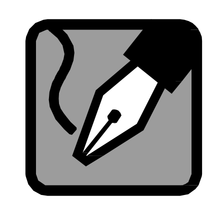
Results





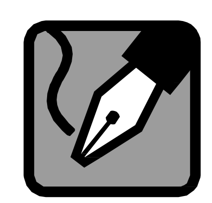
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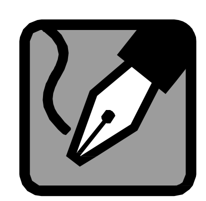
Recommendations





Arabic Summary





Summary and Conclusion



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Islam Atia Eldeeb

Introduction

Rhinitis is a global health problem that affects 20%-40% of the population in developed countries and whose incidence is rising ***(Fokkens, 2002)***.

It can be induced by different mechanisms and involves several etiological agents Rhinitis has traditionally been classified as allergic rhinitis (AR) and nonallergic rhinitis (NAR) ***(Molgaard et al, 2007)***.

The diagnosis of AR is based on clinical manifestations and supported by a positive result for skin prick test (SPT) or serum immunoglobulin E (IgE) antibodies to aeroallergens ***(Bousquet et al, 2008)***.

In contrast, rhinitis is diagnosed as nonallergic when an allergic cause has been ruled out by the presence of an inconsistent clinical history, a negative SPT, and the absence of serum IgE antibodies ***(Warlow et al, 2000)***.

Nonallergic rhinitis is a very heterogeneous group of conditions that can be subdivided into several phenotypes, the largest of which are idiopathic rhinitis and nonallergic rhinitis with

eosinophilia syndrome (NARES) ***(Settipane, 2003).***

It is important to differentiate between AR and NAR، as management differs for each.

In recent years, several studies have shown that many patients previously diagnosed with NAR or idiopathic rhinitis (IR) develops local allergic rhinitis (LAR) or entopy (***Webb et al, 2002).***

Since the first evidence reported by Huggins and Brostoff ***(Huggins et al, 1975)***in 1975, further research has supported the concept of local production of IgE antibodies in the nasal mucosa of patients with allergic rhinitis (AR) and nonallergic rhinitis (NAR) ***(Coker et al, 2004).***

These findings have been furthered with the identification of local allergic rhinitis (LAR) ***(Rondon et al, 2008)*** as a condition involving a localized nasal allergic response in the absence of systemic atopy; ''entopy'' was the first term used to describe this phenomenon ***(Powe et al, 2003).***

This entity is characterized by the following: local production of sIgE antibodies, a TH2 pattern of mucosal cell infiltration during natural exposure to aeroallergens, ***(Powe et al, 2004)*** and a positive response to nasal specific allergen provocation test (NAPT) ***(Wedback et al, 2005)*** manifested by

symptoms and increased levels of sIgE, tryptase, and eosinophil cationic protein (ECP) in nasal secretions ***(Lopez et al, 2010).***

Aim of the work

Our objective is to investigate the prevalence and phenotype of local allergic rhinitis in patients come with clinical manifestations of rhinitis.

Rhinitis

Definition

"Rhinitis" strictly means inflammation of the nasal mucous membranes with inflammatory cell infiltrates. Rhinitis can be more practically viewed as a heterogeneous group of nasal disorders characterized by 1 or more of the following symptoms: sneezing, nasal itching، rhinorrhea, and nasal congestion. ***(Bousquet et al, 2001).***

Classification of rhinitis

From an etiologic point of view, noninfectious rhinitis has been traditionally classified as allergic and nonallergic, and the diagnosis has been based on the clinical history, skin prick test (SPT) responses, and serum IgE levels to inhalant allergens ***(Bousquet et al, 2008).***

However, evidence has recently suggested that this approach is incomplete because patients previously given a diagnosis of NAR or idiopathic rhinitis (IR) might actually be classified as having local allergic rhinitis (LAR) ***(Rondon et al, 2008).***

AR is the most common form of noninfectious rhinitis، but NAR can also affect an important number of patients**.**

However، the exact prevalence of NAR is unknown, and minimal work has been done to identify NAR phenotypes by using standardized methods ***(Bousquet et al, 2008)***.

NAR is a heterogeneous group of nasal conditions،some of which are associated with a particular trigger or cause, although in the majority of patients with NAR, the cause is unknown and the terms IR or vasomotor rhinitis are used to categorize these patients.

Nonallergic rhinitis with eosinophilia syndrome (NARES) is another subgroup of NAR that, because of its characteristic mucosal eosinophilia, is considered a separate nosologic entity. In contrast with IR, patients with NARES respond well to nasal corticosteroids ***(Bousquet et al, 2008)***، but its exact cause remains unknown.

Patients with NAR have been regarded as nonallergic because they have negative SPT responses and absence of serum sIgE ***(Rondon et al, 2007).***

However, over the past decade, several studies have shown that a considerable number of patients with negative SPT responses، negative intradermal skin test results, and lack of serum sIgE who would otherwise have been categorized as having NAR have nasal symptoms after NAPT with a common aeroallergen, including house dust mite (HDM), grass and olive pollen ***(Rondon et al, 2008)***، and possibly others.

Furthermore, recent studies suggest that local production of sIgE occurs in these patients ***(Lopez et al, 2010).***

As a result, the term LAR has been proposed، leading to a new etiologic classification of rhinitis **(Table 1).**

After the description of LAR in patients with a previous diagnosis of NAR, further studies are needed to define the clinical and immunologic differences between IR-NARES and LAR ***(Rondon 2010).***

TABLE I. Etiologic classification of rhinitis

1. Allergic rhinitis
• Allergic rhinitis (with systemic atopy)
i. Classical classification
1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
ii. ARIA classification[14]
1. Duration of symptoms: persistent and intermittent
2. Severity of symptoms: mild, moderate, and severe
• Local allergic rhinitis (without systemic atopy)
i. Classical classification
1. Time of exposure to aeroallergen or aeroallergens: perennial, seasonal, and occupational
ii. ARIA classification[14]
1. Duration of symptoms: persistent and intermittent
2. Severity of symptoms: mild, moderate, and severe
2. Nonallergic rhinitis
• Infectious
• Occupational (irritant)
• Drug induced
• Hormonal
• Irritant
• Food
• Emotional
• Atrophic
• NARES
• Idiopathic

Adapted from Rondón et al.[15]

Allergic rhinitis (AR)

Definition

Allergic rhinitis (AR) is a heterogeneous disorder that despite its high prevalence is often undiagnosed. It is characterized by one or more symptoms including sneezing, itching, nasal congestion, and rhinorrhea. Many causative agents have been linked to AR including pollens, molds, dust mites, and animal dander ***(Bousquet et al, 2008).***

Occurrence rate and prognosis

Rate of occurrence of AR vary depending upon geography, cultural differences, genetics, and environment. Rate of occurrence is obviously more in atopic than non-atopic families and in childhood and young adulthood ***(Norman et al, 1994)***.

Although majority of asymptomatic individuals who produce IgE and respond to skin prick test, never develop AR، about 5–22% have positive skin prick tests, and some of them may develop AR over a period of time .There is a close relationship between skin test positivity and symptoms of AR ***(Droste et al, 1996).***

Rising prevalence of allergic rhinitis

Several hypotheses have been proposed to explain the rising prevalence of AR, as explained below.

Increased allergen exposure

Anthropogenic climate change has been hypothesized as a contributor to rise in the respiratory and skin allergies. Some studies indicate that the present indoor environment is quite favorable to proliferation of allergens. Moreover, there seems to be gene environment interactions. Further studies are needed to address the question of how these interactions contribute to increased prevalence of AR ***(Radon et al, 2004)***.

Reduced immune deviation

Th2 cytokine profile predominates at the birth within the first 5 years of life, transition from a Th2 to a Th1/Th2 cytokine occurs. This “immune deviation” results in the development of a more balanced Th1/Th2 cytokine response in a majority of subjects ***(Prescott et al, 1998)***.

If immune deviation does not occur, then Th2 response remains predominant with a predisposition towards development of allergic diseases. It is unclear whether this occurs as a programmed event related to genetic background, or secondary to antigen exposure in the first few years of life ***(Yabuhara et al, 1997)***

Better hygienic conditions

Improvements of healthcare policy and hygiene standards in developed countries have led to reduction in the occurrence of infectious diseases. The ‘hygiene hypothesis’ proposes association between infection and allergy ***(Wang et al, 2005)***.

Studies supporting this hypothesis show that the risk of developing allergy is inversely related to various markers of infection burden, such as number of older siblings, total number of children in the family, positive serology to orofecal and food borne infections, regular contact with farm animals before the age of 7 years, and attendance at day care facilities. The present increase in vaccinations, early use of antibiotics, use of pasteurized milk instead of un-pasteurized milk, industrialized lifestyle and less number of children in a family result in less exposure to infectious agents ***(Krämer et al, 1999)***.

Lower occurrence of infection causes lower stimulation of cytokines such as IL-12 and interferon-γ, which are important for Th1 activation and microbial destruction. This, together with genetic predisposition causes predominance of Th2 cells over Th1 cells, hence Th1/Th2 balance is disturbed. However, Th1/Th2 model does not explain the phenomenon completely as indicated by studies on helminth infestation ***(Koppelman et al, 2003)***.

Helminthiasis and atopic diseases both exhibit enhanced Th2 response. However, allergic reactions are rarely observed in individuals infected with helminthiasis. Perhaps high serum levels of IgG and IgG4, another Th2 dependent isotype during the parasitic infestation, may protect infected individual from allergy. Indirect support for IgG4 involvement is evidenced by following unrelated facts:

1. Parasite specific IgG4 antibodies inhibit IgE-mediated degranulation of mast cells.

2. Induction of allergen specific IgG4 antibodies is one of the characteristics of successful immunotherapy.

3. High exposure to cat allergens results in high IgG4 levels and decreased atopy when exposed to cat dander ***(Platts-Mills et al, 2001).***

Further, precise studies are required for identification of specific factors which confer protection proposed by the hygiene hypothesis، and their application to the treatment of AR ***(Eder et al, 2004)***.

Genetic factors

Major shift in the gene pool, predisposing more individuals to excessive IgE production has been proposed as a reason for the rising prevalence of AR ***(Howarth et al, 1995)***.

Pathophysiology of allergic rhinitis, cellular and neurological basis

Studies on nasal challenge with allergen/pro-inflammatory mediators following an assessment of cells and mediators released during the course of inflammation have shed some light on the mechanism of AR.

In animal and human models of AR, sequence of events occurs in two phases chronologically termed as early and late phase reactions. Comprehensive view on pathophysiology of AR is illustrated in Fig. 2.


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Fig. 2. Schematic presentation of comprehensive mechanisms of AR. The figure depicts a highly simplified flow diagram of the complex process. Sensitization is a preparation phase where APCs encountering allergen molecule process and present the antigen to T-cells. B cells that have been exposed to antigen produce and secrete IgE, which binds to mast cell receptors. Memory B cells are formed from activated B cells that are specific to the antigen encountered during the primary immune response. On subsequent interaction with the antigen, cross linking of IgE results in degranulation of mast cells. Cytokines cause chemoattraction of other inflammatory cells such as eosinophils and basophils. Neurogenic component is strongly involved in the process of onset, persistence, amplification, and extension to accompanying symptoms such as stress.

Sensitization and early phase reaction

The human upper airway mucosa contains a heterogeneous dense network of antigen presenting cells (APCs) consisting of spatially closely related monocytes/macrophages, and dendritic cells (DCs). The B cell blasts are infrequent. DCs reside in the para- and intercellular channels surrounding the basal epithelial cells and are most effective cells for inducing and regulating the primary immune response ***(Takhar et al, 2005).***

Sensitization of the airway takes place in the conditions of atopy when an inhaled allergen encounters professional APCs in them airway walls. APCs recognize, uptake, and process the antigen into short peptides that associate with major histocompatibility complex (MHC) Class II molecules. APCs also transform naive T helper cells to Th2 cells by means of cytokines such as IL-4 ***(Lambrecht et al, 2001)***.

Th2 cells further produce cytokines such as IL-4 and IL-13, which serve several functions, including promotion of antigen-specific IgE production by B cells. In a process termed as isotype switching, specific B cell subsets transform into plasma cells, which switch from IgM to IgE production Memory B cells play an essential role in maintaining established antibody responses ***(Takhar et al, 2005).***

Upon re-exposure to the same antigen, they are rapidly re-stimulated to proliferate and differentiate into antibody secreting plasma cells that secrete high-affinity antibodies. IgE antibodies “sensitize” a group of cells including mast cells, which originate from bone marrow precursors expressing CD34 molecule. Mast cells express a high-affinity receptor for the Fc region of IgE and therefore IgE binds essentially irreversibly to the mast cells. IgE molecules are specific to one particular antigen. Re-exposure to the same antigen causes its binding on the site situated on the variable region of the IgE molecule bound on mast cell surface ***(Banchereau et al, 2000)***.

Cross-linking of two or more IgE molecules on the mast cell occurs clustering intracellular domains of the cell-bound Fc receptors, leading to a complex sequence of reactions which trigger degranulation of vesicles of mast cells. Subsequently mast cells release a cascade of preformed and newly produced inflammatory mediators resulting in acute airway obstruction. Preformed mediators such as histamine and tryptase released from mast cells cause localized inflammation. This early phase of allergic response in AR is manifested as sneezing، itching, and watery discharge ***(Min et al, 2010).***

Late phase reaction

The mast cell–derived mediators released during early phase responses are hypothesized to act on post capillary endothelial cells to promote the expression of vascular cell adhesion molecule and E-selectin, which facilitate the adhesion of circulating leukocytes to the endothelial cells ***(Naclerio et al, 1985).***

Chemoattractant cytokines such as IL-5 promote the infiltration of the mucosa with eosinophils, neutrophils, and basophils; T lymphocytes; and macrophages ***(Bascom et al, 1988).***

During the 4 to 8 hour period after allergen exposure, these cells become activated and release inflammatory mediators‹ which in turn reactivate many of the proinflammatory reactions of the immediate response. This cellular-driven late inflammatory reaction is termed the "late phase response." This reaction may be clinically indistinguishable from the immediate reaction, but congestion tends to predominate ***(Venarske et al, 2003).***

Eosinophil-derived mediators such as major basic protein, eosinophil cationic protein, and leukotrienes have been shown to damage the epithelium‹ leading ultimately to the clinical and histologic pictures of chronic allergic disease. Subsets of the T-helper lymphocytes are the likely orchestrators of the chronic inflammatory

response to allergens. TH2 lymphocytes promote the allergic response by releasing IL-3, IL-4, IL-5, and other cytokines that promote IgE production, eosinophil chemoattraction and survival in tissues, and mast cell recruitment ***(Durham et al, 1995).***

Cytokines released from TH2 lymphocytes and other cells may circulate to the hypothalamus and result in the fatigue, malaise, irritability, and neurocognitive deficits that commonly are noted in patients with AR. Cytokines produced during late phase allergic responses can be reduced by glucocorticoids ***(Sim et al, 1995).***

When subjects are challenged intranasally with allergen repeatedly, the amount of allergen required to produce an immediate response decreases.

This effect is termed "priming" and is hypothesized to be a result of the influx of inflammatory cells that occurs during late phase allergic responses ***(Smith, 2001).***

The response is clinically significant because exposure to an allergen may promote an exaggerated response to other allergens. Priming highlights the importance of fully defining the spectrum of allergens for a given patient and the need to prevent this process by initiating preseasonal, prophylactic, anti-inflammatory therapy ***(Venarske et al, 2003)***.

Relationship between neurogenic pathways and immunobiology of allergic rhinitis

Neurotransmitters contribute significantly to pathogenesis of AR by altering secretions, smooth muscle tone, vasodilatation, as well as cellular recruitment. Further, neurogenic mechanisms play an important role in orchestration of allergic reactions ***(Wiggers et al, 2008)***.

Activation of peripheral terminals of sensory neurons by local depolarization، axonal reflexes, or dorsal root reflexes causes release of neurotransmitters which act on target cells in the periphery such as mast cells، immune cells, and vascular smooth muscles producing inflammation characterized by redness and warmth due to vasodilation, swelling due to plasma extravasation, and hypersensitivity due to alterations in the excitability of certain sensory neurons ***(Gu et al, 2008).***

This phenomenon is known as "neurogenic inflammation". Symptomatically, coughing and sneezing reflexes in AR and asthma are the important manifestations of and evidence to involvement of neurogenic pathways in these conditions ***(Watkins et al, 1995).***

There appears to be a functional bi-directional communication between mast cells and

the peripheral nervous system. Mast cells are often present in close proximity with nerves.

Mast cell-derived mediators such as histamine cause neuropeptide release from the afferent neurons, which further stimulates mast cells to release their contents. Other mediators such as bradykinin, PGE2, and LTD4 can sensitize and activate sensory nerve endings by inhibiting neuronal after-hyperpolarization and increasing phosphokinase C phosphorylation of neuronal ion channels ***(Gu et al, 2008)***.

Exposure of nerve endings to cytotoxic proteins such as MBP and ECP, and increased expression of neuronal receptors induced by cytokines such as IL-1βand TNF-α may also increase neuronal hyper-excitability ***(Wiggers et al, 2008).***

This illustrates how signaling of neurons in the area of inflammation is influenced by an immune cell released mediator. Peptidergic neurons innervate upper airway structures like submucosal glands, vessels, and epithelium. Studies on capsaicin have helped in understanding the role of neuropeptides in AR and asthma ***(Holzer, 1991).***

Repetitive application of this vanniloid alleviates symptoms of AR. Acute application of capsaicin to the nasal mucosa activates sensory neurons resulting in release of neuropeptides such as Substance P (SP) and calcitonin gene-related

peptide (CGRP), and symptoms of burning, congestion, and rhinorrhea***(Holzer, 1988)***.

It has been shown that intranasal application of histamine in the nasal mucosa of guinea pigs causes induction of SP. Furthermore, allergen challenge in sensitized animals is known to cause release of SP, neurokinin A, and vasoactive intestinal peptide along with other neurotransmitters. Its content in tissues is often correlated with the frequency of sneeze suggesting a role for SP in early phase reaction. SP can induce IL-1 a well-known cytokine in the airway inflammation. Binding of SP to NK1 receptors has been associated with transmission of stress signals, pain, contraction of smooth muscles and inflammation ***(Seto et al, 2005)***.

Also, involvement NK1 receptor has been suggested in mucous secretion and plasma protein extravasation with consequent bronchial obstruction in the airways ***(Kudlacz et al, 1998).***

These evidences imply that modulation of neuropeptides can be an effective way to alleviate the neurogenic inflammation. Among present treatments, corticosteroids have been shown to reduce neurogenic inflammation by inhibiting the synthesis of neuropeptides such as tachykinins by repression of preprotachykinin-A gene, reduced expression of tachykinin receptors، and increased expression of neutral endopeptidase which degrades tachykinins ***(Barnes et al, 1998)***.

Production of inflammatory cells in the bone marrow may be influenced by neurotrophic factors, indicating a role of neurogenic component in this fundamental aspect of AR.

Nerve growth factor (NGF), a neurotropin in conjunction with hematopoetic cytokines can influence the growth and differentiation of eosinophils and basophils. NGF is present in the nasal fluids of individuals with chronic AR and is also acutely released upon nasal allergen challenge ***(Sanico et al, 2000).***

NGF is capable of causing acute effects that change neuroterminal function and produces signals that increase neuropeptide content in nerves and stimulate nerve growth. Overall, evidences as discussed above suggest that important interactions between neural and inflammatory mechanisms take place in AR. These interactions are so significant to believe that the AR results from interplay between cellular inflammation and equally important neurogenic inflammation ***(Seto et al, 2005)***.

Classification

The Allergic Rhinitis and its Impact on Asthma working group (ARIA) re-classified AR in relation to symptom severity, duration and impact of disease on life.

AR can be thus subdivided in intermittent (symptoms less than 4 days per week or less than

4 weeks) and persistent disease (symptoms more than 4 days per week or more than 4 weeks) and further characterized as mild or moderate/severe ***(Bousquet et al, 2001)*** (Figure 2).

This classification has been recently validated in children through an epidemiological survey involving 1275 children between 6 and 12 years.

The historical classification of AR as seasonal or perennial in relation to triggering environmental allergens is useful in some geographical regions and is important for pollen immunotherapy and has been maintained additionally in the British Society of Allergy and Clinical Immunology (BSACI) UK classification of AR. ***(Bousquet et al, 2001).***

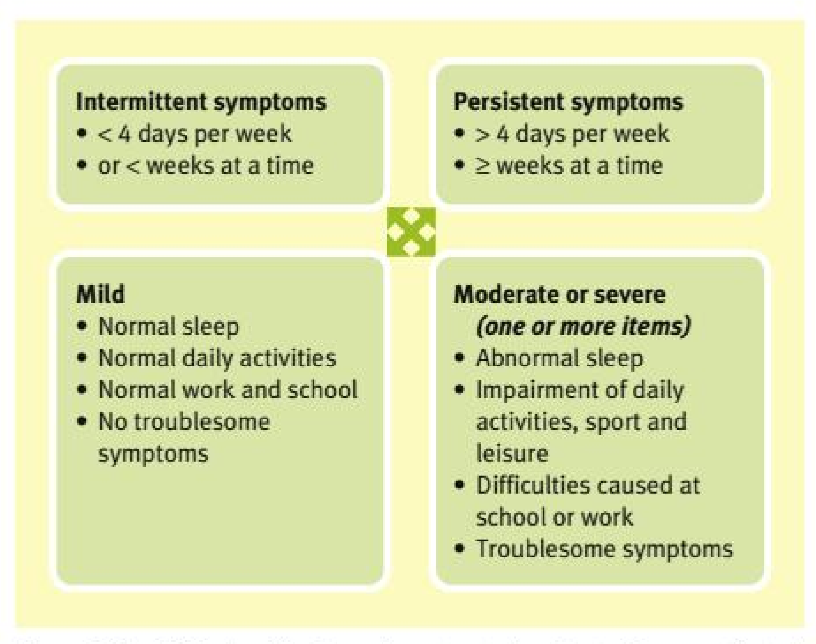


Figure 2 The ARIA classification — in untreated patients. Bousquet J et al: JACI 2001.

Diagnosis of allergic rhinitis

Often treatment of AR is initiated on initial diagnosis of symptoms and/or allergen-specific test**.** The most common diagnostic tests for identifying atopy and the particular allergen(s) involved are skin test and allergen-specific immunoglobulin E (IgE) antibody test. Other tools used to diagnose AR are nasal provocation testing, and nasal cytology using e.g. blown secretions, scraping, lavage, and biopsy ***(Douglass et al, 2006)***.

Skin testing is one of the easiest, most sensitive, and least expensive way to diagnose AR, It helps to identify the allergen. It is done by intradermal allergen administration followed by assessment of edema and redness at the site of antigen injection. Quantification of allergen specific IgE antibody can be undertaken by radioallergosorbent test (RAST) ***(Douglass et al, 2006)***.

RAST is recommended when skin testing is not practical or not available, and when medications interfere with skin testing e.g. antihistamines and tricyclic antidepressants, or when skin testing is contraindicated e.g. severe eczema. However, RAST is not as sensitive as skin test and is more expensive ***(Agency for Healthcare Research and Quality, 2002).*** Referral for nasal endoscopy may be indicated for unresponsive cases of AR, or assessment of nasal polyps, crusting in the nasal cavity, serosanguinous discharge, or if rhinosinusitis, and nasal perforations and ulcerations are suspected. Imaging (X-ray, CT, and MRI) tests may be useful for some cases of suspected sinusitis or sinus polyps.

Differential diagnosis

It is important to consider rarer conditions that can mimic AR. Primary ciliary dyskinesia (PCD) should be suspected when chronic rhinitis

with muco-purulent secretion manifests from birth.

Single sided nasal blockage in toddlers, particularly when associated with purulent discharge, can suggest the presence of a foreign body or unilateral choanal atresia (a malformation in which the nasal fossa does not open onto the aero-digestive system). Unilateral watery rhinorrhea can be secondary to a CSF leak. The detection of nasal polyps in childhood suggests the possibility of cystic fibrosis and should instigate relevant investigations. Hormonal rhinitis can occasional be detected in adolescents on oral contraceptives ***(Ait-Khaled et al, 2009).***

Treatment of allergic rhinitis

There are four general principles for clinical management of allergy: avoidance of allergens/triggering factors, use of appropriate pharmacotherapy, evaluation of need for immunotherapy and its use where appropriate, patient education and follow-up ***(Barnes, 1998).***

Whenever practical, allergen avoidance should be adopted as an integral part of AR management. Avoidance of source of allergens can be based on allergen test of an individual patient. There are a number of recommendations for a step-wise approach to the management of AR. Practice Parameter Recommendations, its updates, and the ARIA (Allergic Rhinitis and its Impact on

Asthma) guidelines can be referred for further information on this subject ***(Sanico et al, 2000)***.

Irrespective of intensity of the disease, symptomatic treatment using different drugs is the mainstay of management of AR:

1. Small molecule pharmacotherapy

Control of symptoms, preventing sequel and improvement of patient's quality of life are the primary goals of pharmacotherapy of AR.

Present treatment strategies aim either to reduce the effect of local release of mediators from the activated cells, or end organ effects of released mediators. As the interplay of several mediators and variety of inflammatory cells is present in the AR, therapies targeting single mediator are not efficient to resolve all the different symptoms, or underlying inflammation ***(Tashiro et al, 2004)***.

Hence, combining drugs with different mode of action can offer highest relief. Presently، different major classes of drugs available for the treatment of AR are: antihistamines, corticosteroids, antileukotrienes, decongestants, mast cell stabilizers, and an anticholinergic agent ***(Tashiro et al, 2004)***.

These drugs act by different molecular mechanisms to reduce symptoms of AR. In the subsequent discussion, drugs available for the clinical treatment, molecular basis of their action,

rational for their use، and prospects are presented in brief:

a. Antihistamines

Antihistamines competitively bind to histamine H1 receptors causing reduced vascular permeability, smooth muscle contraction، mucus secretion, vasodilation, and pruritis leading to relief of sneezing, itching, and rhinorrhea. Antihistamines can reduce constitutive activation of receptors in the absence of histamine and shift equilibrium towards inactive state of the receptor, thus more appropriately these agents are inverse agonists ***(Leurs et al, 2002)***.

First generation antihistamines are widely available over-the-counter, effective and economical, however, their usefulness is limited by their potential to induce sedation due to significant penetration into the brain and leading to various degree of drowsiness and performance impairment in 10–40% of users. Anticholinergic effects such as drying of mucous membranes, urinary retention, constipation, tachycardia, and blurred vision may preclude their use in elderly patients ***(Bachert, 2002)***.

Antagonism of serotonin receptors has significance from the point of view of long term use of these drugs, as it is generally associated with weight gain ***(Tashiro et al, 2005).***

Terfenadine and astemizole were the earliest second-generation antihistamines with low CNS penetration. However, due to their potential for induction of arrhythmia in susceptible individuals, these agents were withdrawn from the clinical practice ***(Tashiro et al, 2004)***.

Loratadine and cetirizine are commonly used less-sedating antihistamines. These agents have good efficacy and low propensity for several troublesome side effects, due to their low brain penetration and better specificity for histamine H1 receptors, Levocetirizine, an enantiomer of cetirizine also has potential to induce sedation at recommended doses ***(Dykewicz et al, 1998).***

The other two agents, fexofenadine and desloratadine are active metabolites of terfenadine and loratadine, respectively and are referred sometimes as third generation antihistamines.

Fexofenadine is classified as non-sedating antihistamine under the USFDA definition. It does not cross blood–brain barrier significant, do not impair wakefulness, psychomotor functions (e.g. driving performance), or do not exacerbate the effect of alcohol. Desloratadine has very weak anticholinergic effect, and is less sedating ***(Tashiro et al, 2004)***.

Antihistamines have antiallergic and anti-inflammatory actions. Receptor-independent effects are exerted via stabilization of mast cell and basophil membrane (inhibition of transmembran

eflux of calcium and intracellular cAMP) leading to inhibition of inflammatory mediators such as histamine, tryptase, and prostaglandins. This property might contribute substantially to the clinical efficacy of antihistamines in the treatment of allergic diseases ***(Bahekar et al, 2008).***

However, all antihistamines do not cause significant mast cell stabilization at therapeutic concentrations, Ketotifen, olopatadine, azelastine, bepotastine and alcaftadine are dual action drugs shown to have H1 receptor antagonism as well as mast cell stabilization at therapeutic concentrations, and these drugs are available as topical agents. Some anti-inflammatory effects may be brought about by histamine H1 receptor antagonism. E.g. modulation of transcription factors NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and GATA3 by H1 receptor antagonism leads to suppression of cytokines and adhesion molecules. It is suggested that an inhibition of inflammatory cell activation may be dependent on histamine H1 receptor blockade these receptor-dependent anti-inflammatory effects may actually be clinically relevant and can be induced by all H1 antagonists. For instance, low concentrations of desloratadine have been shown to inhibit the production of Th2 cytokines IL-4 and IL-13***(Nettis et al, 2005)***.

Topical treatment of antihistamines has advantage of delivering high local concentration this increases the scope for higher anti-

inflammatory effect and reduces the systemic exposure, thereby reducing the potential for systemic side effects. However, reduction of associated symptoms of conjunctivitis, suboptimal delivery, and patient noncompliance may make oral administration necessary in many cases ***(Schroeder et al, 2001)***.

b. Corticosteroids

Intranasal corticosteroids

Intranasal corticosteroids are the most effective medications for treating allergic rhinitis. In most studies, intranasal corticosteroids are more effective than the combined use of an antihistamine and a LT antagonist ***(Pullerits et al, 2002).***

The clinical response does not appear to vary significantly between intranasal corticosteroids that are currently available ***(Kaszuba et al, 2001)***.

The onset of therapeutic effect of intranasal corticosteroid occurs between 3 and 12 hours ***(Meltzer et al, 2001).***

The as-needed dosing (which equated to 55% to 62% of days) of an intranasal corticosteroid (fluticasone propionate) has been shown to be effective in the treatment of seasonal allergic rhinitis but may not be as efficacious as continuous use ***(Dykewicz et al, 2003).***

In 1 study, PRN use of an intranasal corticosteroid (fluticasone propionate) was superior to PRN use of an oral antihistamine (loratadine) for seasonal allergic rhinitis ***(Kaszuba et al, 2001).***

Intranasal corticosteroids are also effective in the treatment of nonallergic rhinitis, especially NARES and vasomotor rhinitis ***(Banov et al, 1994).***

Intranasal corticosteroids may also benefit ocular allergy symptoms associated with allergic rhinitis. Intranasal corticosteroids when given in recommended doses are not generally associated with clinically significant systemic side effects. Studies in both children and adults have failed to demonstrate any consistent, clinically relevant effect from intranasal corticosteroids on the hypothalamic-pituitary-adrenal (HPA) axis, ocular pressure or cataract formation, or bone density ***(Galant et al, 2003).***

In children, growth effect may be a better indicator of systemic effect than HPA axis suppression. The transient effect on growth suppression that has been demonstrated in children after administration of intranasal corticosteroids is dependent on the specific intranasal corticosteroid, and the dose administered, technique used for measuring growth, time of administration, and concomitant use of oral or inhaled corticosteroid. Studies with intranasal fluticasone propionate,

mometasone furoate, and budesonide have shown no effect on growth at recommended doses compared with placebo and reference values (at as much as 2 times the recommended doses) ***(Gradman et al, 2007).***

Growth suppression from intranasal corticosteroids has been reported only with long-term use of beclomethasone dipropionate that exceeded recommended doses or administration to toddlers ***(Guilbert et al, 2006).***

Local side effects of intranasal corticosteroids such as nasal irritation, bleeding, and nasal septal perforation ***(Cervin et al, 1998)*** are rare and can be avoided with proper administration technique. The patient should be periodically examined to assure that these side effects are not present. Preparations containing propylene glycol and benzalkonium chloride may result in local irritation or ciliary dysfunction, respectively ***(Naclerio et al, 2003).***

Systemic corticosteroids

Oral corticosteroids, prescribed for a few days, may be required for the treatment of very severe intractable rhinitis or nasal polyposis ***(Joos et al, 2005).***

The use of parenteral and intraturbinate injections of corticosteroids is discouraged ***(Iglesias et al, 2005).***

c. Antileukotrienes

LT receptor antagonists (LTRAs) are effective in the treatment of seasonal and perennial allergic rhinitis ***(Patel et al, 2005).***

There is no significant difference in efficacy between LTRA and antihistamines (with loratadine as the usual comparator), and their concomitant use may be additive ***(Wilson et al, 2004).***

However, not all studies with the concomitant administration of an antihistamine and a LTRA have shown an additive effect. Although the concomitant administration of a LTRA and an antihistamine can have an additive effect, in general this approach is less efficacious than administering intranasal corticosteroids as monotherapy. However, such combination therapy may provide an alternative treatment for patients who are unresponsive to or not compliant with intranasal corticosteroids ***(Rodrigo et al, 2006).***

Montelukast has an excellent safety profile and has been approved down to 6 months of age. As many as 40% of patients with allergic rhinitis have coexisting asthma. Because montelukast has been improved for both rhinitis and asthma, it may be considered in such patients ***(Barnes et al, 2005).***

The combination of montelukast and a second-generation antihistamine may protect against

seasonal decrease in lung function in patients with allergic rhinitis ***(Keskin et al, 2006).***

d. Nasal decongestants

These drugs reduce blood flow by their agonistic action at α1and α2-adrenergic receptors on endothelial cells of nasal capacitance vessels and are useful in reducing nasal congestion associated with mucosal swelling. Turbinate swelling is reduced by contracting the sphincters that control the blood supply to the venous plexuses in the turbinates. Decongestants are most helpful when combined with an antihistamine ***(Small et al, 2007)***.

The catecholamines pseudoephedrine and phenylephrine are available as orally administered drugs. These agents have been reported to be somewhat effective at reducing rhinorrhea; however, they have no effect on sneezing, pruritis, or ocular symptoms ***(Small et al, 2007).***

The imidazoline derivatives oxymetazoline, xylometazoline and naphazoline are available as intranasal agents. Intranasal decongestants have rapid onset and fewer systemic side effects, however overuse of these agents may cause rebound congestion upon withdrawal. In addition to decongestant effect, anti-inflammatory properties of these agents have been depicted e.g. oxymetazoline has also been shown to cause inhibitory effect on T cell activation, and

inhibition of secretion of cytokines such as IL-1β, TNF-α, IL-6, and IL-8 ***(Ramey et al, 2006)***.

The therapeutic benefit of oxymetazoline can be explained in part by its immunomodulating effect

Adverse effects of topical formulations of decongestants include nasal burning, stinging, dryness, and occasionally mucosal ulceration. Systemic side effects including nervousness, insomnia, irritability, headache, tachycardia, hypertension, increased intraocular pressure, and aggravation of urinary obstruction are more relevant to oral agents. This coupled with their potential for tolerance and rebound congestion underscores the need or sensitive, short-term, or intermittent use of decongestants for the management of AR ***(Tuettenberg et al, 2007).***

e. Mast cell stabilizers

Re-exposure to a previously met allergen leads to its binding on IgE antibodies attached to mast cell Fc RI receptors. This causes crosslinking of Fc RI receptors, whereupon mast cells synthesize and degranulate mediators such as histamine, tryptase, leukotrienes، and proteases.

This is most crucial step in the allergic cascade once secreted, inflammatory mediators cause further recruitment of inflammatory cells such as eosinophils, neutrophils, basophils, and

macrophages to the site of inflammation ***(Stenton et al, 1998)***.

Synthesis and expression of a plethora of cytokines (IL-1, IL-3, IL-4, IL-5, IL-13, TNF-α) and chemokines (IL-8, GM-CSF, MCP-1, RANTES) by mast cells have profound influences on leukocyte biology, and allergic inflammation. Therefore, stabilization of mast cells is an important therapeutic intervention in the treatment of AR.

Intranasal cromolyns have been shown to inhibit the degranulation of mast cells by impeding the function of chloride channels important in regulating cell volume and preventing extracellular calcium influx into the cytoplasm of mast cells ***(Gschwentner et al, 1996).***

Cromolyns have been shown to inhibit both early- and latephases of the allergic reaction***)***. When used prophylactically، cromolyns can prevent as well as treat the symptoms of AR. In addition to their effects on mast cells, cromolyns inhibit migration or survival of macrophages, eosinophils, monocytes, and platelets ***(Holgate ST, 1998)***.

Minor side effects such as nasal burning, stinging, or sneezing have been reported in 10% of the patients. The dual antihistamine/mast cell stabilizer olopatadine is the most widely used topical agent for symptomatic relief of AR

(Stenton et al, 1998). Bepotastine besilate is under clinical development.

f. Topical anticholinergic agents

Parasympathetic stimulation of nasal glands causes vasodilation resulting in watery secretion mediated through the autonomic transmitter acetylcholine. Muscarinic receptor blockade through anticholinergic drugs inhibits mucous secretion, rhinorrhea, reduces congestion and sneezing. These drugs would be available only for the topical application for obvious safety reasons ***(Yanez et al, 2012).***

Ipratropium bromide is a prototype intranasal anticholinergic agent. On topical application‹ plasma concentrations of ipratropium bromide have been shown to be less than the levels where systemic anticholinergic effects are known to occur. Dry mouth/throat, dizziness, ocular irritation‹ blurred vision, conjunctivitis, hoarseness, cough, and taste perversion have been reported inb2% users of topical ipratropium bromide ***(Wood et al, 1995)***.

The ARIA guidelines suggest its use in rhinorrhea, without benefit for other symptoms of AR ***(Brozek et al, 2010).***

2. Therapies based on immunomodulation

a. Allergen specific immunotherapy

Immunotherapy induces desensitization to specific allergens. Allergen specific immunotherapy causes increase in IgG4/IgE ratio, inhibits recruitment and activation of inflammatory cells, and restores the imbalance between Th2 and Th1 phenotypes, mainly by the induction of regulatory cytokines such as IL-10. In subcutaneous immunotherapy (SCIT), extract of allergens is injected subcutaneously with increasing doses until a maintenance dose is reached ***(Passalacqua et al, 2009)***.

Systemic immunization can induce severe systemic allergic reactions limiting its use. To reduce the risk of anaphylaxis induced by SCIT, oral, nasal، bronchial, epicutaneous, and intraepithelial routes are also being investigated. Sublingual immunotherapy (SLIT) has low incidence of adverse reactions and has convenience of self-administration ***(Incorvaia et al, 2010)***.

However, it is not as effective as SCIT in reducing the symptoms. In fact, intra-lymphatic injection of allergens has been shown to be much more effective than SCIT.

Desensitization tablets for a majority of allergens triggering over 80% of allergies: grass pollen, house dust mites, birch pollen, ragweed

pollen, and Japanese cedar pollen are being developed by Stallergenes ***(Senti et al, 2008).***

Oralair a sublingual tablet for desensitization to grass pollen, was marketed in Germany for adults in 2008, and for children in 2009. Stallergenes recently reported the first results of its new phase IIb/III clinical trial conducted to test a sublingual immunotherapy with birch pollen rBet v 1 (recombinant Bet v 1).

The allergy vaccine Pollinex Quattro Ragweed, for the treatment of AR due to ragweed pollen is under development by Nycomed. Further, omalizumab, an anti-IgE mAb, may have potential to increase safety and efficacy of immunotherapy ***(Incorvaia et al, 2010)***.

Activation of the innate immune system through toll-like receptor agonists with and without specific allergens appears to improve the immunologic responses and clinical outcomes in patients with allergic diseases. The use of chemically altered allergens, allergoids, recombinant allergens, and relevant T-cell epitope peptides has produced positive results ***(Kim et al, 2008).***

b. Monoclonal anti-IgE antibody

The recombinant, humanized, monoclonal anti-IgE antibody omalizumab forms complexes with circulating IgE at Ce3 domain، blocking its interaction with high affinity receptors on mast cells and basophils ***(Holgate et al, 2005)***.

In a large pivotal trial, omalizumab decreased serum-free IgE levels and provided clinical benefit in a dose dependent fashion in patients with seasonal AR ***(Kaliner, 2004)*** and perennial AR ***(Chervinsky et al, 2003)***. In adults and adolescents, omalizumab was found to decrease nasal symptoms and improve Rhinitis Quality of Life Questionnaire (RQLQ) in patients with birch and ragweed pollen induced AR, or those sensitized to outdoor allergens ***(Adelroth et al, 2000)***.

This antibody was well tolerated with a low rate of anaphylaxis ***(Cox L, et al, 2007)*** (1000/0.9).

The clinical benefit of treatment with omalizumab is associated with its effect on cellular markers in the blood and nasal tissue ***(Plewako et al, 2002)***, and with a reduction in mast cell FcεRI expression and function. Co-treatment of omalizumab with specific immunotherapy is known to be even more effective ***(Kopp et al, 2009)***.

Use of omalizumab will remain restricted to treatment resistant AR ***(Beck et al, 2004)*** primarily

due to its potential for anaphylaxis, increased risk of cancer and its high cost.

3. Capsaicin desensitization, complementary, alternative treatments، and surgeries

Capsaicin interacts at vanilloid receptors expressed by nasal C fibers. Repeated application of capsaicin to skin or mucosal surfaces causes desensitization of peripheral nerve endings. Such an approach can be used for the treatment of neuropathic pain and other conditions such as vasomotor rhinitis, where neuropeptides play a major role. By optimizing the dose of capsaicin, its neurotoxic effects can be differentiated from other effects ***(Szallasi, 1996)***.

In rabbit model of AR capsaicin has been shown to alleviate nasal congestion، rhinorrhea and sneezing and reduce sensory neuron sensitivity of the mucosa. Capsaicin desensitization of human nasal mucosa has been shown to reduce symptoms of AR ***(Stjärne et al, 1998)***.

Other study reported non-significant effect of capsaicin in the perennial AR to house dust mite ***(Gerth et al, 2000)***.

Pretreatment with local anesthesia can be undertaken to avoid local pain and irritation caused by capsaicin application. Thus far, limited documented data exist to determine capsaicin

therapy for AR. Nasal irrigation with saline or hypertonic saline has been used in the complementary management of AR. The procedure involves rinsing the nasal passages with a salt–water solution. The procedure helps to rid the pharynx and sinus cavities of allergens and mucus ***(Zhang et al, 1999).***

It serves to reduce tissue swelling in the nasal passages, and is known to produce a significant improvement in symptoms and signs. In children, saline nasal irrigation allowed for the use of lesser doses of topical corticosteroids without compromising symptoms ***(Li et al, 2009).***

Decreased exposure to microbes in childhood is suggested to play a crucial role in the maturation of host immune system. Exposure of microbial flora early in life allows for a change in the Th1/Th2 balance, favoring Th1 response. In line with this, probiotic therapy involving ingestion of live beneficial microorganisms can potentially modulate toll-like receptors and the proteoglycan recognition protein of enterocytes, leading to activation of dendritic cells and a Th1 response ***(Flohr et al, 2005).***

Evidences suggest that Bifidobacteria and Lactobacilli given orally may lead to a balanced T-helper-cell response, and stimulate production of IL-10 and TGF-β, both of which have a role in the development of immunologic tolerance to antigens and can decrease allergic-type immune responses.

Some studies show positive effect of probiotic use in AR ***(Isolauri et al, 2000)***.

For instance, Lactobacillus paracasei-33 caused increase in quality of life parameters , Bifidobacterium longum BB536 caused relief in rhinorrhea, nasal blockage and composite scores, and reduction in ocular and nasal symptoms in Japanese cedar pollinosis, Lactobacillus gasseri altered serum IgE concentration, Lactobacillus casei DN-1 14 001 reduced number of AR episodes in children with AR ***(Michail, 2009).***

However, others showed little clinical benefit of probiotics use ***(Koyama et al, 2010).*** Insufficient and non-robust data available so far clearly warrants further research to support use of probiotics in the treatment of AR.

Acupuncture is a traditional Chinese therapeutic approach based on “meridian system to correct core imbalances in order to disperse blocked Qi and blood”. The procedure uses insertion and manipulation of needles into various points on the body. Moxibustion, a form of heat treatment involves burning of a cone of medical herbs on acupuncture points. Results of acupuncture in the treatment of AR are inconclusive, due to low quality of partial inclusion literatures ***(Xiao et al, 2009)***.

Intranasal phototherapy using combination of UV-A, UV-B and visible light has been suggested as the effective modality in the

treatment of AR, especially in cases where commonly used drugs are contraindicated and/or have insufficient efficacy. Significant improvement in the symptoms of AR has also been claimed in one study after far infrared radiation (FIR) therapy ***(Hu et al, 2007).***

FIR with an invisible electromagnetic wave of wavelength between 5.6 and 1000μm is perceived as heat by thermo-receptors. Different mechanisms including increase in microcirculation have been proposed to explain beneficial effects of FIR. Surgical procedures are considered to address certain complications, or concomitant conditions. These include conditions such as sinusitis not relieved by medications, nasal polyps, enlarged turbinates, and deviated nasal septum causing severe nasal obstruction، and other complications such as non-resolving ear fluid ***(Arunachalam et al, 2000).***

Non allergic rhinitis (NAR)

Definition

Non-allergic rhinitis is defined as rhinitis symptoms in the absence of identifiable allergy, structure abnormality or sinus disease ***(Smith, 2003)***.

There have been many terms to describe non-allergic rhinitis which include vasomotor rhinitis, vascular rhinitis, perennial, chronic and noninfectious perennial rhinitis, among others**.**

Causes

Occupational

Arises from airborne agents at a patient's workplace, these agents do not act through *immune* mediated systems, but are an irritant to the nasal mucosa and cause hyper responsive reactions. They trigger both the Olfactory nerve and the Trigeminal nerve that senses burning and irritation by airborne chemicals . There have been over 205 different chemical identified as irritants. They include cigarette smoke, solvents like chlorine, metal salts, latex, glues and wood dust. These patients usually present with a concurrent occupational asthma ***(Settipane et al, 2001).***

For diagnosis, we use primarily history and nasal provocation with stimuli. About 70% of

patients improve with symptoms when triggers are avoided ***(Settipane et al, 2001) .***

Drug Induced Rhinitis

There are a variety of medications that can cause rhinitis when administered either orally or topically. These drugs can be divided into two main groups as pharmacologic or aspiring hypersensitivity .

Here is that include many of the drugs that are common causes rhinitis:

- Cocaine
- Topical nasal decongestants
- Alpha-adrenoceptor antagonists
- Reserpine
- Hydralazine
- Angiotensin-converting enzyme inhibitors
- Beta-blockers
- Methyldopa
- Guanethidine
- Phentolamine
- Oral contraceptives
- Non-steroidal anti-inflammatory medications
- Aspirin
- Psychotropic agents
- Thioridazine
- Chlordiazepoxide

- Chlorpromazine
- Amitriptyline
- Perphenazine
- Alprazolam
- Sildenafil (Viagra)

Many common antihypertensive medication and psychiatric medications cause rhinitis ***(Bachert et al, 2004).***

These are infrequent but predicable side effects. They usually lead to congestion, but PND and watery secretions can be other symptoms.

PDE-5 inhibitors like Sildenafil (Viagra) cause allergic rhinitis by inducing engorgement of the nasal mucosa including the turbinates . Intolerance to ASA or NSAIDS is unpredictable. However, they predominately cause rhinorrhea. ASA rhinitis may be a part of the ASA triad of hyperplasic rhinosinusitis, nasal polyps and asthma ***(Scadding et al, 2001)***.

Rhinitis Medicamentosa

Rhinitis medicamentosa (RM) is a condition that caused by overuse of topical nasal steroids. Also known as rebound or chemical rhinitis, the incidence is somewhere between 1-9% of non-allergic rhinitis and it is more common in younger adults and pregnant women ***(Jones et al, 1997) .***

To understand the cause of RM, we must first look at some of the basic science behind the

nasal mucosa. The mucosa is innervated by sympathetic fiber that release norepinephrine ، which stimulate alpha 1 and alpha 2 receptors, This in turns causes vasoconstriction .

The sympathomimetic amines and imidazoline derivatives (phenylephrin and oxymetazoline, respectively) both produce vasoconstriction by endogenous release of norepinephrine .The problem arises with prolonged use, this leads to reduced production of norepinephrine in the presynapes and decreased sensitivity of the alpha receptors in the postsynapes, which in turn requires higher doses for shorter acting time ***(Blom et al, 1997).***

This cycle of excess dose use and decrease symptomatic relief will lead to worsening of the original symptoms .The risk of RM is greatest after 10 days use of medications, Treatment includes gradual stopping of decongestant with introduction of topical corticosteroid. This will lead to a temporary increase in symptoms and patents should be warned beforehand of this and to not restart the original medication. Patients should be off the medication for 3 months before starting any other surgical or medical treatment for the original nasal disease ***(Dockhorn et al, 1999).***

NARES

NARES (non-allergic rhinitis with eosinophilia syndrome) is another non-allergic entity that is defined as rhinitis without allergic cause but has 20-25% eosiniophils seen on nasal smears. As with the other NAR disease, there is lack of allergy by skin test or IgE antibodies ***(Erhan et al, 1995).***

Prevalence is 13-33% of NAR, NARES etiology is unknown. However, it is believed to be associated with the ASA triad as NARES patients tend to develop asthma and nasal polyps later in life and they tend to have abnormal prostaglandin metabolism ***(Erhan et al, 1995).***

And yet, eosinophilic counts are elevated in 20% of the nasal smears in the general population and not everyone with eosinophilias have symptom of rhinitis .

Recent studies by *Powe et al (2001)* show that NARES is a local IgE mediated response that does not result in a systemic response. They found that 50% of non-allergic rhinitis patient that had a negative skin prick test were found to have positive result to nasal allergy challenge ***(Powe et al, 2001).***

Therefore, skin prick test negative patient with eosinophilia may require allergen challenge nasally before diagnosis of non-allergic rhinitis. This is important to know, because NARES is a

subset of non-allergic rhinitis who responds better to nasal corticosteroids than other nonallergic rhinitis groups ***(Powe et al, 2001).***

Hormonal Rhinitis

Hormonal rhinitis (HR) is defined as rhinitis during period so known hormonal imbalance. Estrogens are known to affect the autonomic nervous system by increasing a host of factor including parasympathetics, acetyl choline transferase, and acytycholine content, and also increase inhibition of sympathetic system. Therefore, the most common causes are pregnancy ‹menstruation, puberty and exogenous estrogen. With pregnancy, HR usually manifests in the second month and will continue throughout pregnancy ***(Rondon et al, 2009).***

Hypothyroidism is also known to cause hormonal rhinitis. In hypothyroidism, increase TSH release causes edema of the turbinates. Nasal congestion and rhinorrhea are the most common symptoms of RH ***(Shusterman et al, 2009).***

Idiopathic rhinitis

Next we come to Idiopathic rhinitis (IR). This is also known as vasomotor rhinitis and is characterized by nasal blockage and rhinorrhea, with some sneezing and pruritis. Etiology is unclear, with failed attempts to differentiate by hyperactivity to histamine, methacholine, cold air or capsaicin. IR is solely diagnosed by patient

complaints and therefore a diagnosis of exclusion ***(Sander et al, 2009).***

The exclusion criteria include: having positive skin test, smoking, nasal polyps، pregnancy, medications affecting nasal function, and good response to nasal steroids. Pt who have a good response to nasal steroids tend to have NARES ***(Sander et al, 2009) .***

IR is not believed to be caused by inflammation. IR patients have no significant increase in mucosal lymphocytes, antigen presenting cells, eosinophils, macrophages, mast cells or IgE positive cells compared to controls. And studies have shown a reduction in immunocompetent cells in the mucosa of IR pt after treatment with nasal steroids did not reduce nasal complaints ***(Powe et al, 2001) .***

Others

Finally we come to the last group of NAR, the other category. There are a number of conditions that can produce the same signs and symptoms of rhinitis. These include structural conditions like deviated septum, nasal tumors, enlarged adenoids or turbinates, and atrophic rhinitis. One must also look for mimicker like Wegener's, sarcoidosis, and polychondritis ***(Bachert et al, 2004) .***

Diagnosis

To provide an accurate diagnosis, one must always start with complete history and physical exam .Here are some pertinent questions to ask with the history :

•What are your nasal an sinus symptoms and do they include discharge، congestion، PND ، sneezing، itching?

•Do you have environmental allergies, undergone skin testing, or been treated for allergies?

•Are there certain situations, environment in which symptoms are worse like home, work ، indoors, outdoors, times of the year or day?

•What is your work, are there exposures to chemicals?

• Do your symptoms begin with medications or do any medications help your symptoms?

•Do you have asthma, allergy to aspirin, or any sinus polyps?

•Have you undergone any sinus surgeries?

With the physical exam, one should do a nasal endoscopy.

Boggy, edematous mucosa suggests non infections, while inflammation and purulent discharge from middle meatus suggests infection ***(Rondon et al, 2007) .***

Treatment

The key to treatment is patient education, Teach patient to avoid triggers, have them change their environment, change their medication. If these are not feasible, then medical therapy is the next course of action ***(Slavin et al, 1999) .***

Immunologic therapy has no benefit to non-allergic rhinitis and therefore it is important to distinguish the disease before considering immunotherapy. Nasal lavage has been shown to have minor decongestion benefits and improves mucocilliary function ***(Grafet al, 1996) .***

Topical nasal steroids have been used widely for use with NAR. Fluticasone, budesonide and beclomthasone are the only ones approved by FDA for use in NAR. However, efficacy is inconsistent and use must be for a minimum of 6 wks. With the exception of NARES, topical steroids do not provide the same relief as they do with allergic rhinitiss ***(Arikan et al, 2006).***

Antihistamines have given us inconsistent results. Histamine release is the main pathophysiology for allergic rhinitis and therefore, not a good consideration for NAR. Azelastin intranasal have been proven efficacious for all

forms of NAR, including Idiopathic rhinitis. It is an H1 receptor antagonist that also inhibits synthesis of leukotrienes, kinins, cytokines and free radicals. The exact mechanism behind its relief is unknown ***(Webb et al, 2002).***

Anticholinergic drugs also have their place in treatment. Ipratropium bromide has been shown to be effective with rhinorrhea symptoms. The strength used is 0.03% with 2 sprays TID initially. The dose is slowly lowered to one spray BID as maintenance .

Mast cell stabilizers such as cromolyn have been shown to have no benefit with nonallergic rhinitis. There have been no studies that have looked at leukotriene modifies in the treatment of non-allergic rhinitis ***(Graf et al, 1997) .***

Capsaicin has been shown to be of benefit to idiopathic rhinitis. This is the main chemical with in hot peppers.

This substance is known to activate C-fiber in the nose which is responsible for pain. With repeated application of capsaicin, a desensitization and degeneration of c-fibers occur. A five dose treatment of high dosages at 1 hr intervals has been shown to work as well as five high dose treatments over 2 wks. Up to 75% of patients will show long lasting relief. There are lower dose capsaicin formulation nasal sprays that are available OTC at pharmacies that can be used in higher frequencies ***(Incaudo et al, 2001)*** .

Surgery is used only for failed medical treatment. Although nasal polyps and septal deviation do not cause NAR, they can cause problems with medications reaching its desired goal and therefore should be corrected .

Silver nitrate has been studied as therapy. Given topically, it has been shown to down regulate stimuli of the mucosa. Clinical trials show improvement over placebo and anosmia was shown to be rare side effect. A 20% solution was applied by cotton tip for 1 minute once a wk for 5 wks ***(Incaudo et al, 2001)*** .

Vidian Neurectomy has been demonstrated as treatment modality. Since 1961, it has been used successfully to relieve rhinorrhea, initially done transantral, it has been moved to transnasally by endoscopy. Efficacy is up to 88***% (Jacobs et al, 2009).***

Turbinate reduction has also been beneficial. In a randomized control trial of 382 pt، with 6 yr follow up, a sub-mucus resection with lateral displacement has been found to be better in term of efficacy to turbinectomy, laser, cryotherapy, or electrocautery ***(Blom et al, 1997) .***

Recently, *Ikeda et al (2006)* has shown benefit to a combined vidian neurectomy with inferior turbinate resection for treatment of chronic rhinitis .

Follow up

Follow up is key for patient with non-allergic rhinitis. In a recent study by ***(Rondon et al, 2009)*** non-allergic rhinitis patient shown previously to have no sensitization to rest were found to sensitized to allergens on follow up. As many as 24% of the patient were found to develop sensitization this suggest that sensitization may appear later in the course of rhinitis disease ***(Rondon et al, 2009).***

Local allergic rhinitis (LAR)

Definition

Local allergic rhinitis (LAR) is a localized nasal allergic response in the absence of systemic atopy characterized by local production of specific IgE (sIgE) antibodies, a TH2 pattern of mucosal cell infiltration during natural exposure to aeroallergens and a positive nasal allergen provocation test response with release of inflammatory mediators (tryptase and eosinophil cationic protein) ***(J Allergy Clin Immunol, 2012)***.

Prevalence and effect

Although true prevalence data are not available, results generated in various European centers suggest that among patients with negative SPT responses and undetectable IgE antibodies in serum، LAR might be present in 47% to 62.5% of patients with perennial and seasonal symptoms. Many of these patients were given a diagnosis of IR or NARES previously. These data indicate that LAR might be a common, although underestimated entity ***(Lopez et al, 2008).***

Large studies in adults and children using consensus procedures for NAPTs, nasal secretion collection, and laboratory analytic techniques are needed to determine the epidemiologic characteristics of LAR. These studies should also

define in more detail whether LAR has 1 or more unique clinical phenotypes، including comorbidities, which can distinguish it from other forms of nasal disease. For example, is it possible that LAR represents a relatively mild condition that responds well to pharmacologic rhinitis treatment leading to a diminished prevalence in specialty clinic populations, or is the opposite true? ***(Rondon et al, 2007)***.

An important consideration in assessing the prevalence of LAR is the influence of the environmental allergen load. Is this entity more frequent in some areas because of different levels of aeroallergen exposure?

Also, are other environmental cofactors eg, (air pollution, temperature, and humidity) influencing the development of LAR as opposed to conventional AR? Answers to these questions require multicenter epidemiologic studies in geographic areas with a different environmental allergen load and varying atmospheric conditions ***(Lopez et al, 2010)***.

Information published thus far has identified a few highly prevalent allergens as LAR culprits. These have primarily included HDM, grass, and olive pollen ***(Lopez et al, 2010)***.

However, it is not yet known whether other common allergens or less frequent or unusual allergens are also involved. Other allergens to be considered include molds, animal dander,

occupational allergens, and possibly others. Interestingly, in an article by Carney et al، of 13 patients with presumed LAR, only 1 responded to nasal provocation with a dog/cat allergenic extract mixture. Substantial methodological difficulties will have to be surpassed to provide an adequate answer to this question. These include the determination of optimal allergen doses for NAPTs and the development of more practical methods to conduct nasal allergen challenges ***(Carney et al, 2002)***.

Pathophysiology

A characterization of pathophysiologic mechanisms (endotypes) and clinical manifestations (phenotypes) is needed for a better understanding of LAR. As stated above, the pathophysiology is described in more detail below:

Local production of sIgE and inflammatory mediators in patients with AR and NAR

Several authors have studied the concept of local production of IgE in nasal mucosa of patients with AR. Platt-Mills ***(Platts-Mills, 1979)*** showed increased levels of rye grass sIgE in nasal secretions of patients with AR, Durham et al ***(Durham et al, 1997)*** found expression of ε germline gene transcripts and mRNA for the ε heavy chain of IgE in nasal B cells, and further research has demonstrated the existence of class-switch recombination to IgE in nasal mucosa of patients with AR ***(Coker et al , 2003)***.

After the detection of nasal sIgE in patients with NAR ***(Huggins et al, 1975)*** the presence of nasal sIgE in patients with LAR with perennial and seasonal symptoms during natural exposure to aeroallergens in as many as 22% in the former cases and 35% in the latter cases was demonstrated by Rondon et al.

The possible reasons for not detecting sIgE in a high proportion of patients with LAR with a positive NAPT response might be the low sensitivity of the determination assays used by the dilutional effect of nasal lavage; the lack of inclusion of occult allergen or allergens; the existence of another immunologic mechanism, such as the possibility of nonspecific protease activity stimulation of HDM on airway innate immune cell; and others ***(Rondon et al, 2008)***.

The development of a noninvasive in vitro diagnostic technique with high sensitivity in detecting nasal sIgE would be a breakthrough in the diagnosis and screening of LAR.

More evidence supporting the local synthesis of sIgE in the nasal mucosa of patients with NAR has recently been reported، although no studies have yet been carried out in patients with LAR ***(Powe et al, 2010)***.

Powe et al have demonstrated the localization of free light chains (FLCs) in tissue and nasal secretions of patients with AR and patients with NAR and proposed that they could

function to mediate hypersensitive immune responses involving mast cells. Further investigation is needed to establish whether FLCs have an adjuvant or independent role in patients with IgE-mediated allergy and to elucidate the presence of FLCs in patients with LAR.

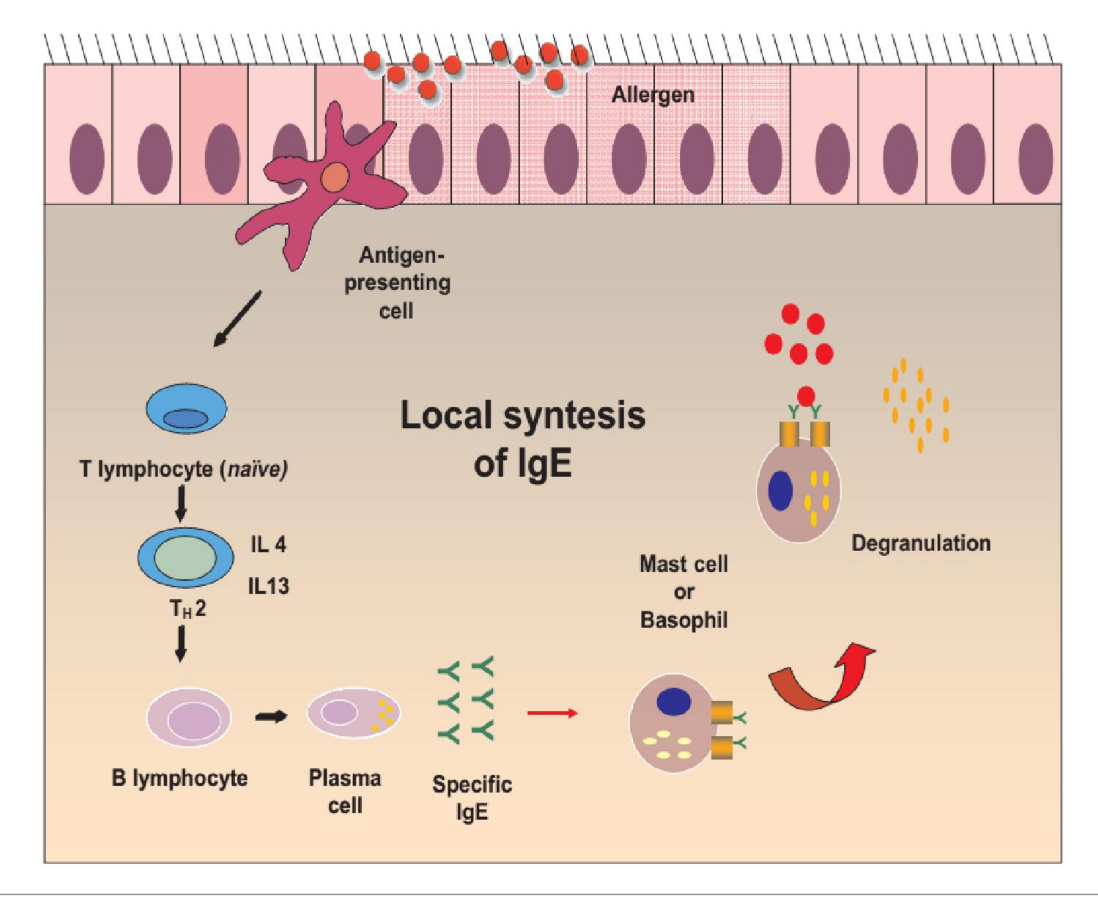


Figure 1. The IgE-mediated hypersensitivity response proposed in allergic rhinitis classically restricted to lymphoid tissue has been shown to occur in nasal mucosa. Ig indicates immunoglobulin; IL, interleukin; T_H, helper T cell.

TH2 nasal inflammatory pattern

Although the cause of IR is unknown, several pathophysiologic mechanisms have been proposed; including inflammatory and neurogenic mechanisms and changes in mucosal permeability. ***(Bousquet et al, 2008)*** the importance of an inflammatory mechanism in patients with NAR has been controversial in the past. Although several histologic and in situ hybridization studies found a TH2 inflammatory pattern with increased numbers of mast cells, eosinophils, IgE, B cells ***(Huskisson et al, 2001)*** and T cells, other studies found no significant differences between patients with NAR and control subjects. ***(van Rijswijk et al, 2003)***.

These apparent contradictory results might be explained by the heterogeneity of NAR and the recent diagnosis of LAR in nonatopic subjects. These early studies included patients with a different pathogenesis, predominantly inflammatory in patients with NARES and possibly in patients with LAR***, (Powe et al, 2004)*** and neurogenic mechanisms in patients with IR or vasomotor rhinitis***(Rondon et al, 2007)***.

Recently, the existence of a nasal TH2 IgE-mediated inflammatory response has been confirmed in patients with LAR ***(Rondon et al, 2008)***.

Flow cytometric studies in nasal lavage fluid demonstrated that patients with LAR and

those with AR had a similar leukocyte-lymphocyte phenotype with increased levels of eosinophils, basophils, mast cells, CD3 T cells and CD4 T cells during natural exposure to aeroallergens ***(Rondon et al, 2008)***. Moreover, more than 70% of patients with NAR and LAR presented criteria for NARES (nasal eosinophils >20%).

Previously, Powe et al ***(Powe et al, 2004)*** found an increase in CD8 rather than CD4 T-cell numbers both in patients with NAR and patients with AR compared with numbers seen in control subjects and reduced numbers of antigen-presenting cells in patients with IR compared with those seen in patients with AR.

In this study sIgE antibodies were not determined, and furthermore, no NAPTs were performed. Therefore the number of patients with LAR and their pathophysiologic characteristics were not evaluated.

Positive NAPT responses

Several studies have demonstrated that more than 47% of patients given a previous diagnosis of IR had LAR with positive NAPT responses monitored based on subjective (symptoms) plus objective parameters acoustic rhinometry**,** anterior rhinomanometry and nasal secretion of sIgE and inflammatory mediators***(Lopez et al, 2010)***.

The results showed that activation of mast cells and eosinophils and IgE production were induced after nasal stimulation with aeroallergens. Patients had an immediate or dual response to NAPTs accompanied by release of tryptase, ECP, and sIgE in nasal secretions. The kinetics study of tryptase showed a strong correlation with nasal itching and sneezing and a pattern of release that varied with the type of response ***(Rondon et al, 2009)***.

Immediate responders presented with significantly higher levels of tryptase at 15 minutes and 1 hour after challenge compared with baseline values, whereas dual responders showed significantly increased levels from 15 minutes to 6 hours ***(Rondon et al, 2009)***.

Lopez et al confirmed these results in patients with perennial LAR with positive NAPT responses to Dermatophagoides pteronyssinus. An important finding in both studies was the detection of a progressive increase in the levels of nasal sIgE from 1 to 24 hours after an NAPT. This rapid secretion of sIgE after challenge, with basal detection of sIgE in some patients, supports the existence of a persistent local production of sIgE in nasal mucosa that rapidly increases after allergen stimulation ***(Lopez et al, 2010)***.

All these findings have led researchers to consider the need to evaluate whether local production of sIgE in patients with other

apparently nonallergic respiratory diseases, such as chronic rhinosinusitis with or without nasal polyps*, (Sabirov et al, 2008)* asthma, ***(Campo et al, 2011)*** or conjunctivitis, could exist.

Local IgE production associated with nasal polyps

Nasal polyposis is a chronic inflammatory process of the nasal and sinus mucosa of unknown cause. In the last years, research has demonstrated that Staphylococcus aureus might modify airway disease by inducing synthesis of polyclonal IgE antibodies against super antigen from S aureus and environmental allergens in nasal polyp tissue ***(van Zele et al, 2007)***.

This polyclonal mucosal production of IgE against several antigens (aeroallergens or not) constitutes a model of local IgE synthesis different from LAR, in which the specific antibodies to aeroallergens are correlated with the allergic clinical response and specific activation of B cells, mast cells, and eosinophils and are commonly associated with low total nasal IgE levels. However, the clinical relevance of these findings needs to be established ***(van Zele et al, 2007)***.

Local IgE production associated with asthma

Evidence suggests an overlap between atopic and non-atopic asthma. Increased numbers of B cells undergo IgE heavy chain class-switch recombination, ***(Takhar et al, 2007)*** with an

increase in IL4 and IL5 mRNA expression in lung tissue from both atopic and nonatopic asthmatic patients.

CLINICAL MANIFESTATIONS

Patients with LAR often present with symptoms typical of AR (ie, rhinorrhea, obstruction, sneezing, and itching), which are often associated with ocular symptoms, and good response to oral antihistamines and nasal corticosteroids ***(Rondon et al, 2009)***

Patients with LAR and systemic AR report anterior rhinorrhea, sneezing, and itching as the most frequent symptoms ***(Lopez et al, 2008).***

Patients with LAR can be grouped according to the classical (seasonal, perennial, and occupational) and Allergic Rhinitis and its Impact on Asthma (intermittent and persistent) classifications at the same time because they do not overlap. The former is based on time of exposure to allergens, whereas the latter is based on persistence of symptoms ***(Bousquet et al 2008)***.

The majority of patients with LAR studied reported persistent rhinitis with moderate-to-severe symptoms frequently associated with conjunctivitis (25% to 57%) and asthma (33% to 47***%) (Rondon et al, 2011).***

DIAGNOSTIC APPROACH

Diagnosis of LAR can be confirmed based on the detection of nasal sIgE, a positive NAPT response, or both in the absence of systemic atopy. Nasal lavage is a noninvasive method for the study of cells, inflammatory mediators, and other immunologic markers ***(J Allergy Clin Immunol, 2012)***.

Determination of sIgE levels in nasal lavage fluid has proved useful for detecting local sensitization both during natural exposure and after NAPTs. This in vitro test has a high specificity but a low sensitivity of 22% to 40% ***(Rondon et al, 2008)***.

Whether the dilution effect، a nonspecific response to HDM, other factors, or both, might contribute to this low sensitivity must be evaluated. A nasal allergen provocation test with a single aeroallergen (NAPT-S) is a very useful diagnostic tool in patients with LAR with higher sensitivity than determination of nasal sIgE, tryptase, or ECP levels ***(Lopez et al, 2010)***.

However, it is a very time-consuming technique، and its use might be limited in daily clinical practice. For this purpose, a new protocol of NAPTs with multiple aeroallergens in one session has proved to be useful, specific, sensitive, reproducible، and less time-consuming for the screening of patients with LAR ***(Rondon et al, 2007)***.

The sequential application of several aeroallergens in one session did not produce any irritant response and showed 100% concordance with the gold standard NAPT-S, achieving 75% reduction in the total number of visits required for final diagnosis in the NAR group and 55% reduction in patients with LAR compared with NAPT-S results ***(Rondon et al, 2011).***

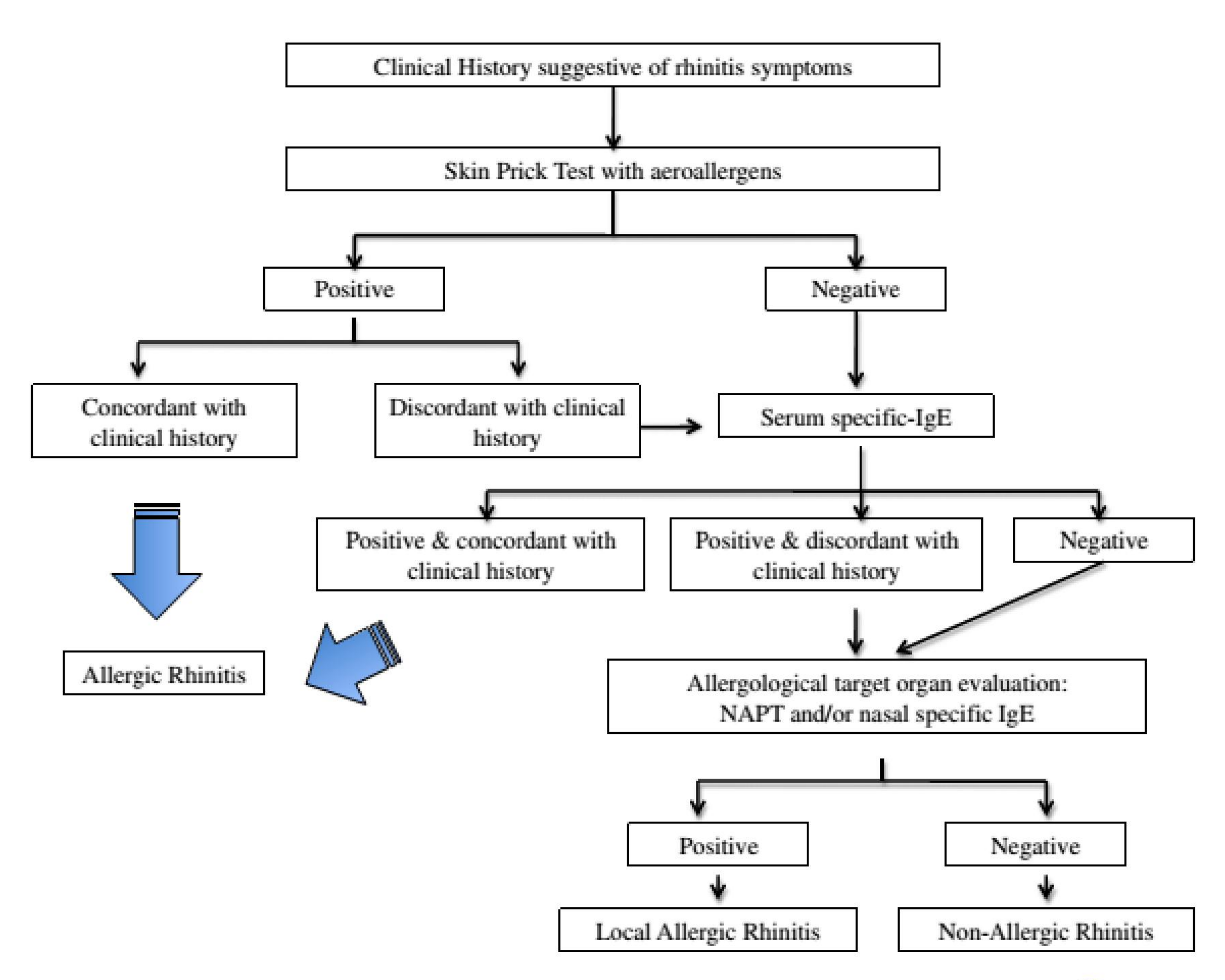


FIG 2. Diagnostic approach in patients with LAR. Adapted from Rondón et al.[15]

❖ ***Nasal allergen provocation test:***

An allergen extract or other provocative agents is instilled intranasally and the intensity of nasal symptoms such as itching, sneezing, rhinorrhea and nasal obstruction occurred are recorded.

Distant symptoms, such as ocular and bronchial ‹can be observed as well ***(Fokkens et al, 2007).***

Allergen administration

Before challenging the nose by allergen extract, both nasal cavities should be examined to identify nonspecific anatomical variations of nasal patency caused by the nasal cycle ***(Bachert et al, 1997)***.

Nonspecific nasal hyper reactivity can also be investigated by challenging the nasal mucosa with isotonic saline sprayed into the wider side of the nose; this should be done as a baseline challenge. Allergens are available in various forms such as solution, powder or pollen grains.

Such allergen can be administered into the nasal cavity by several methods i.e. Pump spray, paper disc, atomizer, pipettes, or dropper. Important issues which have to be considered before delivering allergen are adverse effects, ease of instillation, amount of solution per

delivery and distribution of mast cell in the nose ***(Gosepath et al, 2005)***.

NPT can be performed unilaterally or bilaterally depending on the method of allergen administration. Unilateral challenge may be easier but bilateral challenge should give higher number of positive reactions. According to our current knowledge of nasal physiology, unilateral challenge should also provide relevant information regarding the intensity of the nasonasal reflex elicited in the contralateral side of the nose ***(Litvyakova et al, 2002)***.

A better method of delivery could be by using hand-operated nasal spray. With the spray method, a reasonable contact area would be to the anterior part of nasal cavities. Because of ease of use and the predictability of the amount of allergen administered, most of research centers in Europe recommend this method as a standard delivery system***(Bachert et al, 1997)*** Atomizers also generate larger particles which help avoiding aspiration of allergens into the lower airways.

Evaluation

Four cardinal symptoms of allergic rhinitis are assessed before and after instillation of allergen extract into the nasal cavity. They are itching, sneezing, rhinorrhea and nasal obstruction.

Extranasal symptoms such as coughing and ophthalmic symptoms are also recorded ***(Tantilipikorn et al, 2008).***

Scoring system

NPT is considered positive if the nasal airflow decreases by more than 40% of the baseline value ،regardless of the clinical symptom score. It is also considered positive if nasal airflow decreases by greater than 20% of the baseline value, combined with a symptom score greater than 3 ***(Meltzer et al, 1993)*** (Table 3).

Table 3. Scoring system of nasal provocation testing[32]

Symptom	*Severity*	*Score*
Rhinorrhea (judged by examiner)	No secretion	0
	Slightly increase	1
	Profuse	2
Sneezing	0-2 sneezes	0
	3-5 sneezes	1
	More than 5 sneezes	2
Extranasal symptoms	None	0
	Watery eyes	1
	Cough or urticaria	2

THERAPEUTIC OPTIONS

The correct differentiation between LAR and NAR is a key point for the management of this new entity. The management of AR includes the following:

Allergen avoidance, pharmacologic treatment, immunotherapy and education. Patients with LAR have reported a good response to topical nasal corticosteroids and oral antihistamines ***(Bousquet et al, 2008):***

1. Allergen avoidance

The first-line treatment of allergic rhinitis and local allergic rhinitis involves the avoidance of relevant allergens (e.g., house dust mites, moulds, pets, pollens) and irritants (e.g., tobacco smoke) ***(Bousquet et al, 2008)***.

Patients allergic to house dust mites should be instructed to use allergen-impermeable covers for bedding and to keep the relative humidity in the home below 50% (to inhibit mite growth). Pollen exposure can be reduced by keeping windows closed, using an air conditioner, and limiting the amount of time spent outdoors during peak pollen seasons. For patients allergic to animal dander, removal of the animal from the home is recommended and usually results in a significant reduction in symptoms within 4-6 months. However, Small and Kim Allergy, Asthma & Clinical Immunology2011 compliance with this

recommendation is poor and, therefore, the use of high-efficiency particulate air (HEPA) filters and restricting the animal from the bedroom or to the outdoors may be needed to attempt to decrease allergen levels. Measures for reducing exposure to mould allergens include cleaning with fungicides, dehumidification to less than 50%, and HEPA filtration.These avoidance strategies can effectively improve the symptoms of allergic rhinitis, and patients should be advised to use a combination of measures for optimal results ***(Small et al, 2007)***.

2. *Intranasal corticosteroids*

Intranasal corticosteroids are also first-line therapeutic options for patients with mild persistent or moderate/severe symptoms and they can be used alone or in combination with oral antihistamines. When used regularly and correctly, intranasal corticosteroids effectively reduce inflammation of the nasal mucosa and improve mucosal pathology ***(Pullerits et al, 2002).***

Studies and meta-analyses have shown that intranasal corticosteroids are superior to antihistamines and leukotriene receptor antagonists in controlling the symptoms of allergic rhinitis, including nasal congestion, and rhinorrhea ***(Wilson et al, 2004).***

They have also been shown to improve ocular symptoms and reduce lower airway symptoms in

patients with concurrent asthma and allergic rhinitis ***(Dewester et al, 2003).***

The intranasal corticosteroids available are include fluticasone furoate, beclomethasone, fluticasone propionate, triamcinolone acetonide, mometasone furoate, ciclesonide and budesonide ***(Bernstein et al, 2004).***

Since proper application of the nasal spray is required for optimal clinical response, patients should be counseled on the appropriate use of these intranasal devices. Ideally, intranasal corticosteroids are best started just prior to exposure to relevant allergens and, because their peak effect may take several days to develop, they should be used regularly ***(Lee et al, 2009).***

The most common side effects of intranasal corticosteroids are nasal irritation and stinging. However, these side effects can usually be prevented by aiming the Spray slightly away from the nasal septum ***(Small et al, 2007).***

Evidence suggests that intranasal beclomethasone, but not other intranasal corticosteroids, may slow growth in children compared to placebo; however, long-term studies examining the impact of intranasal beclomethasone on growth are lacking ***(Skoner et al, 2000).***

It is important to note that most patients with allergic rhinitis presenting to their primary-care

physician have moderate-to-severe symptoms and will require an intranasal corticosteroid. Bousquet et al. noted improved outcomes in patients with moderate-to-severe symptoms treated with a combination of these agents ***(Bousquet et al, 2003).***

3. __Oral Antihistamines__

The newer, non-sedating, second-generation oral antihistamines (e.g., desloratadine, fexofenadine and loratadine) are the first-line pharmacological treatments recommended for all patients with local allergic rhinitis ***(Small et al, 2003).***

These agents have been found to effectively reduce sneezing, itching and rhinorrhea when taken regularly at the time of maximal symptoms or before exposure to an allergen. Although the older (first-generation) sedating antihistamines (e.g., diphenhydramine, chlorpheniramine) are also effective in relieving symptoms, they have been shown to negatively impact cognition and functioning therefore, they are not routinely recommended for the treatment of local allergic rhinitis ***(Kim et al, 2008)***.

This might be one phenotypic characteristic of patients with LAR in contrast with those with nonatopic rhinitis. Double-blind, placebo-controlled clinical trials will be of interest to compare the effectiveness of pharmacologic

treatment in patients with LAR and those with AR ***(Rondon et al, 2008)***.

An important consideration is whether patients with LAR could benefit from specific treatment, such as immunotherapy.

A pilot observational study has just been carried out by (Rondon et al) in patients with LAR sensitized to grass pollen: Fifty percent of patients were treated with preseasonal grass specific subcutaneous immunotherapy (SCIT) for 6 months and rescue medication in the spring (SCIT group), and the other 50% of patients received rescue medication alone (control group) ***(Rondon et al, 2011)***.

In this study SCIT with grass pollen increased tolerance to the aeroallergen and reduced symptoms and rescue medication in patients with LAR compared with those seen in the control group.

These interesting results highlight the need to conduct phase II double-blind, placebo-controlled clinical trials to evaluate whether LAR might be considered a new indication for specific immunotherapy.

Subject and methods

This cross-sectional study conducted on 120 patients suffering from rhinitis.
The selected patients recruited from the Allergy and Clinical immunology outpatient clinic at Ain Shams University Hospitals.

All patients subjected to the following:

Full detailed allergic history taking and clinical examination with special emphasis on rhinitis symptoms (sneezing, blocked nose, runny nose, and nasal itching/rubbing) in periods without common cold or flu.

Then take history of current medication, limitation of daily activities and sleep disturbance, age of onset of symptoms of rhinitis, suspected precipitating factors, frequency and severity of symptoms and presence of family history of atopic disorders and/or presence of other atopic disorders.

Exclusion criteria:

1- Individuals who give history of systemic atopy.
2- Pregnancy and lactation.
3- Immunological diseases.
4- Chronic rhinosinusitis.
5- Smoking.
6- Vasomotor rhinitis.

7- Patients on NSAIDS.
8- Patients with positive skin prick test and elevated total IgE.

Allergic rhinitis diagnosed according to the criteria set out by allergic rhinitis and its impact on asthma guidelines (ARIA) in 2001.

The frequency of allergic rhinitis classified as intermittent and persistent and the severity classified as mild, moderate and severe, respectively, by the diagnosed criteria set out by (ARIA) in 2001.

After that, we do Skin Prick test, using allergen extracts prepared at the allergy department at Ain Shams University Hospitals.

Serum total IgE level using a sandwich enzyme-linked immunosorbent assay (ELISA) kit (BioCheck, Inc., Foster City, USA).

If both the skin prick test and serum total IgE negative, we do nasal allergen provocation test (NAPT) by the same common aeroallergen done by the skin prick test, after doing (NAPT), we take a nasal secretion sample from the patient and do nasal specific IgE (sIgE) test to it using an enzyme-linked immunosorbent assay (ELISA).

1. Skin prick testing techniques

Skin prick tests are usually performed on the inner forearm. Any number of allergens can be tested, as few as 3 or 4 or up to about 25 allergens.

The following is a brief overview of how the test is performed.

- The arm is cleaned with soap and water or alcohol
- The forearm is coded with a skin marker pen corresponding to the number of allergens being tested. Marks should be at least 2cm apart.
- A drop of allergen solution is placed beside each mark.
- A small prick through the drop is made to the skin using a sterile prick lancet. Excess allergen solution is dabbed off with a tissue

The standard panel of the aeroallergens included (house dust, hay dust, mixed mites, mixed moulds, mixed feather, grases, traw, otton dust, cat epithelium, dog epithelium, goat epithelium, rabbit epithelium, sheep wool, tobacco, pigeon, latex, candida)
In this study we focus on most common 6 aeroallergen which are: (house dust, hay dust, mixed mites, mixed moulds, mixed pollens, and cat epithelium)

In addition to the allergens tested, there should be a positive and negative control. The positive control, usually a histamine solution, should become itchy within a few minutes and then become red and swollen with a

"wheal" in the centre. The negative control, usually a saline solution should show no response. The epidermis was raised without causing any bleeding **(James,2002).**

Interpretation of the test:

Reactions are assessed by the degree of redness and swelling and the size of the wheal produced. The wheal has a white, raised edge that surrounds the swollen red central area of any skin reaction. It usually takes about 15-20 minutes to reach a maximum size, and thereafter fades over a few hours.

A skin test panel was considered valid if the difference in mean wheal diameters between the positive and negative controls was at least 1mm.

A wheal diameter ≥ 3mm more than the negative control was considered positive.

For skin prick tests to be informative, they must be interpreted in conjunction with the patient's history and physical examination **(Liang, 2002).**

2. Serum Total Immunoglobulin E

Sampling

Blood was collected from each patient by withdrawing venous blood by a single puncture technique of the antecubital vein. Samples were dispensed gently into a sterile tube.

Serum was prepared by centrifugation for 10 minutes at 3000 rpm at room temperature, a liquated and stored after labeling at -20°C until analysis. At the time of assay, samples were thawed, mixed and allowed to stand at room temperature for at least 15 minutes.

Principle of the test:

One kit was used for monoclonal antibody specific for total IgE. The monoclonal antibody was pre-coated into the microplates.

Standards and samples were pipetted into the wells, and any total IgE present in standards or samples was bound by immobilized antibody.

After washing away any unbound substances, enzyme-linked monoclonal antibodies specific for total IgE was added to the wells.

Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and a color developed in proportion to the amount of total IgE bound in the initial step. The reaction was stopped and the intensity of color was measured.

3. Nasal allergen provocation test (NAPT)

An allergen extract or other provocative agents is instilled intranasally and the intensity of nasal symptoms such as itching, sneezing, rhinorrhea and nasal obstruction occurred are recorded.

Distant symptoms, such as ocular and bronchial، can be observed as well ***(Fokkens et al, 2007).***

Allergen administration

Before challenging the nose by allergen extract, both nasal cavities should be examined to identify nonspecific anatomical variations of nasal patency caused by the nasal cycle ***(Bachert et al, 1997)***.

Nonspecific nasal hyperactive reactivity can also be investigated by challenging the nasal mucosa with isotonic saline sprayed into the wider side of the nose ***(Gosepath et al, 2005)***; this should be done as a baseline challenge. Allergens are available in various forms such as solution, powder or pollen grains.

Such allergen can be administered into the nasal cavity by several methods i.e. Pump spray, paper disc, atomizer, pipettes, or dropper. Important issues which have to be considered before delivering allergen are adverse effects, ease of instillation, amount of solution per delivery and distribution of mast cell in the nose.

NPT can be performed unilaterally or bilaterally depending on the method of allergen administration. Unilateral challenge may be easier but bilateral

challenge should give higher number of positive reactions. According to our current knowledge of nasal physiology, unilateral challenge should also provide relevant information regarding the intensity of the nasonasal reflex elicited in the contralateral side of the nose ***(Litvyakova et al, 2002)***.

A better method of delivery could be by using hand-operated nasal spray. With the spray method, a reasonable contact area would be to the anterior part of nasal cavities. Because of ease of use and the predictability of the amount of allergen administered, most of research centers in Europe recommend this method as a standard delivery system***(Bachert et al, 1997)*** Atomizers also generate larger particles which help avoiding aspiration of allergens into the lower airways.

Allergen dosage

The lowest allergen concentration should be started from 1:10,000 to 1:5,000 w/vol ***(Gosepath et al, 2005)*** Or 50 allergen unit (AU)/ml or 50-100 protein nitrogen unit (PNU) ***(Riechelmann et al, 2002)***. If the initial concentration does not induce any symptom or clinical signs, then the next concentration is increased by a 3-fold increment, e.g. 1:10,000, 1: 3,000, 1: 1,000. It should be noted that such recommended doses have been applied to European subjects ***(Roongapinun et al, 2005)***.
The test solution is applied into the nose by pointing the device upwards and laterally to deposit allergen solution on the middle and inferior turbinates, while avoiding spraying directly to the back of the nose ***(Gosepath et al, 2005)***.
In our study, we using allergen extracts prepared at the

allergy department at Ain Shams University Hospitals at concentration 1:5.000 then 1:1.000 if no response to the low concentration.

Evaluation

Four cardinal symptoms of allergic rhinitis are assessed before and after instillation of allergen extract into the nasal cavity. They are itching, sneezing, rhinorrhea and nasal obstruction.

Extranasal symptoms such as coughing and ophthalmic symptoms are also recorded ***(Tantilipikorn et al, 2008).***

Scoring system

NPT is considered positive if the nasal airflow decreases by more than 40% of the baseline value، regardless of the clinical symptom score. It is also considered positive if nasal airflow decreases by greater than 20% of the baseline value, combined with a symptom score greater than 3 ***(Meltzer et al, 1993)*** (Table 3).

Table 3. Scoring system of nasal provocation testing[32]

Symptom	*Severity*	*Score*
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	Profuse	2
Sneezing	0-2 sneezes	0
	3-5 sneezes	1
	More than 5 sneezes	2
Extranasal symptoms	None	0
	Watery eyes	1
	Cough or urticaria	2

4. Nasal specific immunoglobulin E (sIgE)

The following is a brief overview of how the test performed:

Specimen collection

After doing the nasal allergen provocation test (NAPT) to the patient, we ask him to sneeze inside a plastic vial and get a nasal secretion sample.
Samples may be stored at 2-8 °C up to several days or up to several months at -20 °C. Sample were allowed to come to room temperature before assayed ***(elshami and alaba, 1989).***

Procedure

All components must be at room temperature (15 - 28°C) before use.

1) 50 µl of each calibrator, control and patient samples was added into the wells prepared.

2) 50 µl of the selected ligand-labeled specific allergen or mixed allergen panel was pipetted to the specified wells.
3) 50 µl of the ligand-labeled anti-IgE Ab was pipetted into the wells prepared for calibrators A through F. A disposable tip was used for the samples and calibrators. The lips were changed between samples and calibrator to avoid carryover contamination. Calibrators must be processed in the first plate of each raw, which can span more than 96 wells.
4) The plate was rotated on the micromix for 1 hour.
5) 50 µl of anti-ligand was added to all wells.
6) The plate again was rotated for 1 hour on the micromix.
7) Decanted, then, the plate was washed 4 times with the microwash, each time with 300µl buffered wash solution.
8) 200 µl of enzyme-labeled anti-IgE Ab was added to every well.
9) The plate was rotated for l hour on the micromix.
10) Decanted, then the plate was washed 4 times with the microwash, each time with 300 µl buffered wash solution. Before TMB substrate was added, the plate was hited on absorbent paper to stroke off all residual droplets.
11) 20 µl of TMB substrate solution was added to all wells.
12) the microplate was read, immediately for 5 minutes in the microplate reader at 650 nm ***(pecquet, 1992).***

Calculation

A standard curve was plotted using log-log graph paper. The average mOD/min of each calibrator on the vertical axis was plotted against concentration on the horizontal axis. A straight-line segments connected adjacent plotted values, then the allergen-specific IgE concentration for the patient samples was estimated by interpolation.

Expected Values

The class member is a semi quantitative index to the amount of endogenous IgE specific for the selected allergen. Qualitative values and interpretation of class results are provided in the table below ***(pecquet, 1992)***:

Class	Ku/l	Interpretation
0	< 0.350	negative
I	0.360 – 0.460	Mild positive
II	0.470 – 0.990	Moderate positive
III	1.00 - more	Strong positive

- Negative results: class 0
- Posative results : class I or greater

Statistical Methods

Quantitative variables were presented as minimum, maximum, mean, standard deviation (SD), median and interquartile range (IQR).

Qualitative variables were presented as number and percentage.

The Pearson chi square test, or Fisher's exact test when appropriate, was used to compare between-group differences as regards nominal variables. For comparison of ordinal variables, the chi square test for linear-by-linear association was used.

The Kruskal Wallis test was used to compare differences among the groups as regards non-normally distributed quantitative variables. The Mann-Whitney U test was used for post hoc comparison whenever the Kruskal Wallis test revealed a statistically significant difference among the groups.

The diagnostic value of biomarkers was examined by construction of two-by-two contingency tables and calculation of the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) rates. Then, the following indices were calculated: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall classification accuracy.

P-values <0.05 are considered statistically significant.

Results

This cross sectional study conducted on 120 adult Egyptian patients with clinical manifestations suggestive of rhinitis (selected from the allergy outpatient clinic at Ain shams university hospitals between March 2013 to March 2014).

The results of this study are listed in the following tables and figures:

Table 1. Age and duration of symptoms

Variable	Minimum	Maximum	Mean	SD	Median	IQR
Age (yr)	14	72	33.6	12.2	31.5	25.0 - 40.5
Duration of symptoms (yr)	0.4	30	6.5	5.9	5.0	3.0 - 8.0

SD, standard deviation; IQR, interquartile range.

This table show that, the age of the patients in our study ranged from 14 years old to 72 years old with mean age 33.6 years old. And the duration of the symptoms range from 0.4 to 30 years.

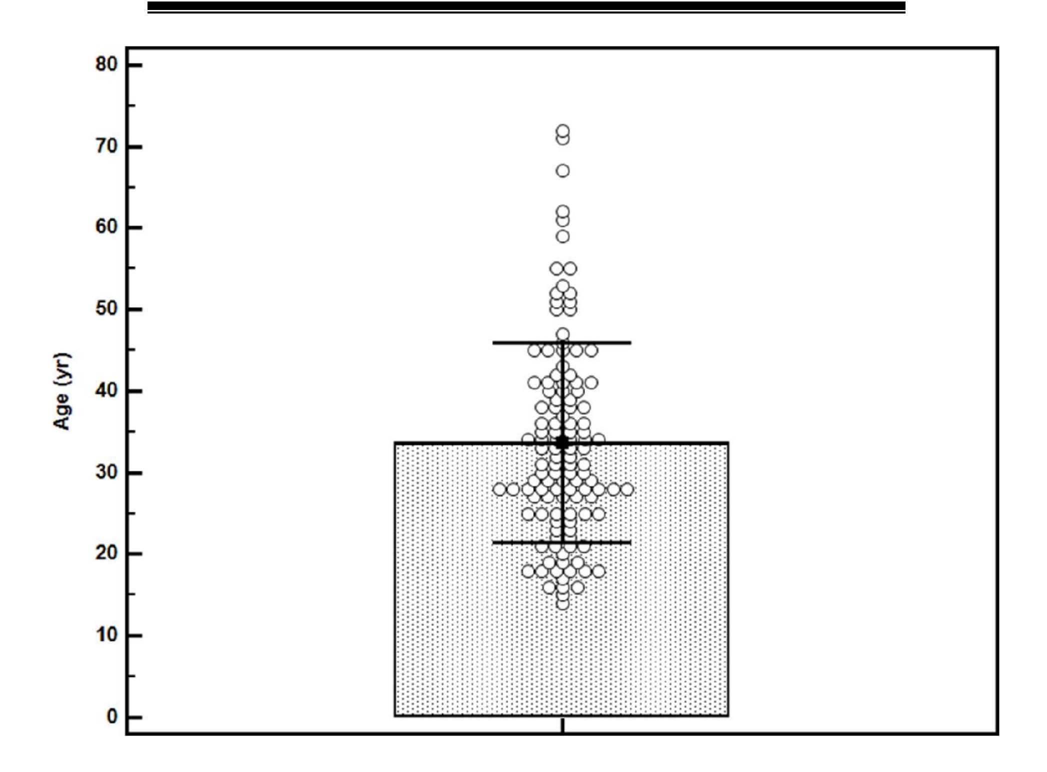


Figure 1. Age distribution in the whole study population. Bar represents mean. Error bars represent standard deviation.

This figure show that, the age of the patients in our study ranged from 14 years old to 72 years old with mean age 33.6 years old.

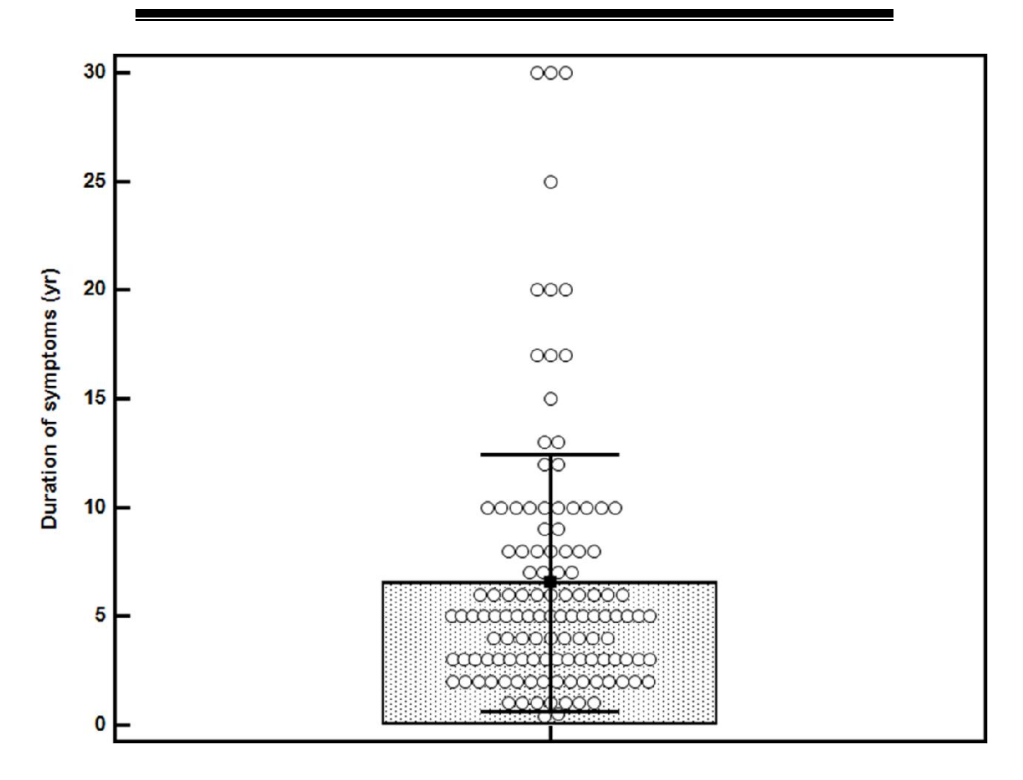


Figure 2. Duration of symptoms in the whole study population. Bar represents mean. Error bars represent standard deviation.

This figure show the duration of the symptoms range from 0.4 to 30 years with mean duration 6.5 years.

Table 2. Gender distribution in the whole study population

		Number	Percent
Gender	*Male*	43	35.8
	Female	77	64.2

This table show that among all 120 patient on this study, the male gender was 43 patient (35.8%) and female gender was 77 patient (64.2%).

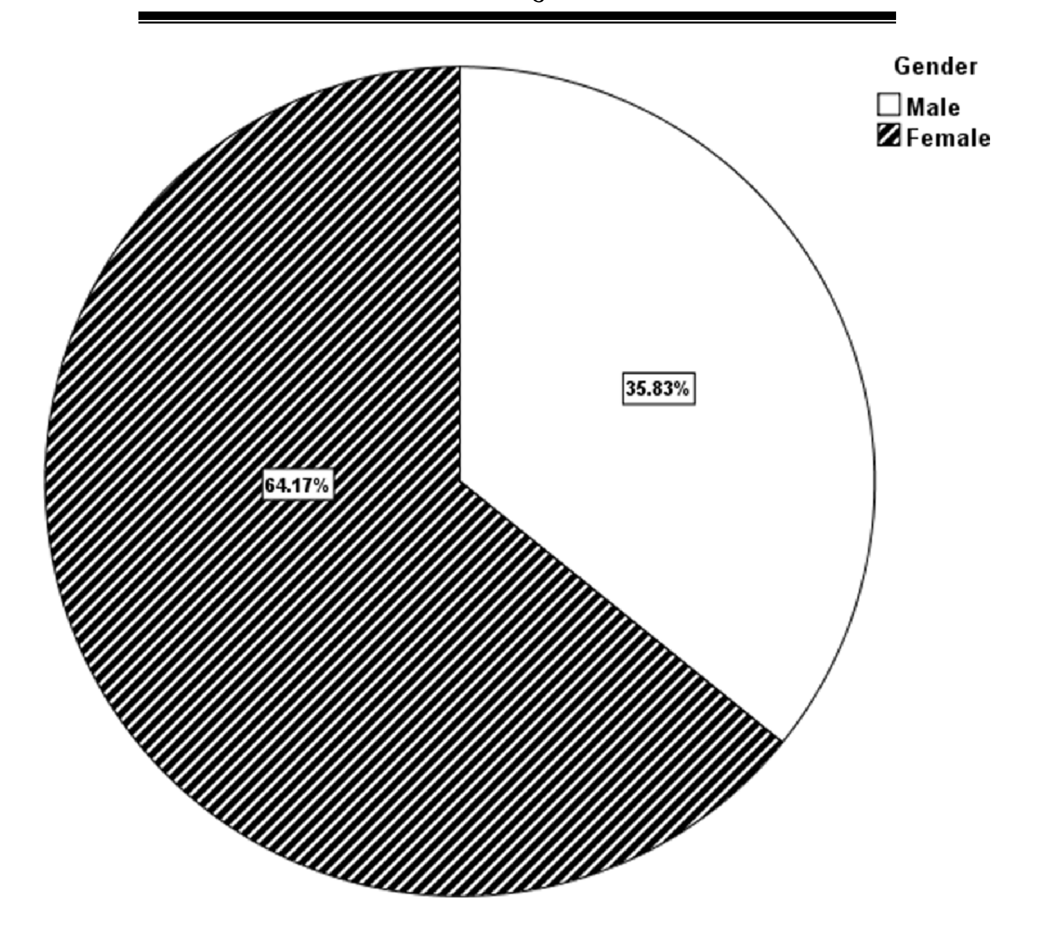


Figure 3. Percentage of either gender in the whole study population.

This figure show that the female gender represent 64.17% in whole study population and the male gender represent 35.83%.

Table 3. Persistency and severity of rhinitis

Variable		Number	Percent
Persistency of rhinitis	*Persistent*	80	66.7
	Intermittent	40	33.3
Severity of symptoms	*Mild*	22	18.3
	Moderate	47	39.2
	Severe	51	42.5

This table show the degree of the frequency and severity of the symptoms of rhinitis according to (ARIA classification 2001), which show that most of them come with persistent frequency (66.7%) and the intermittent frequency come with (33.3%). And majority of them come with severe symptoms (42.5%) then moderate symptoms by (39.2%) and then the mild symptoms come with (18.3%).

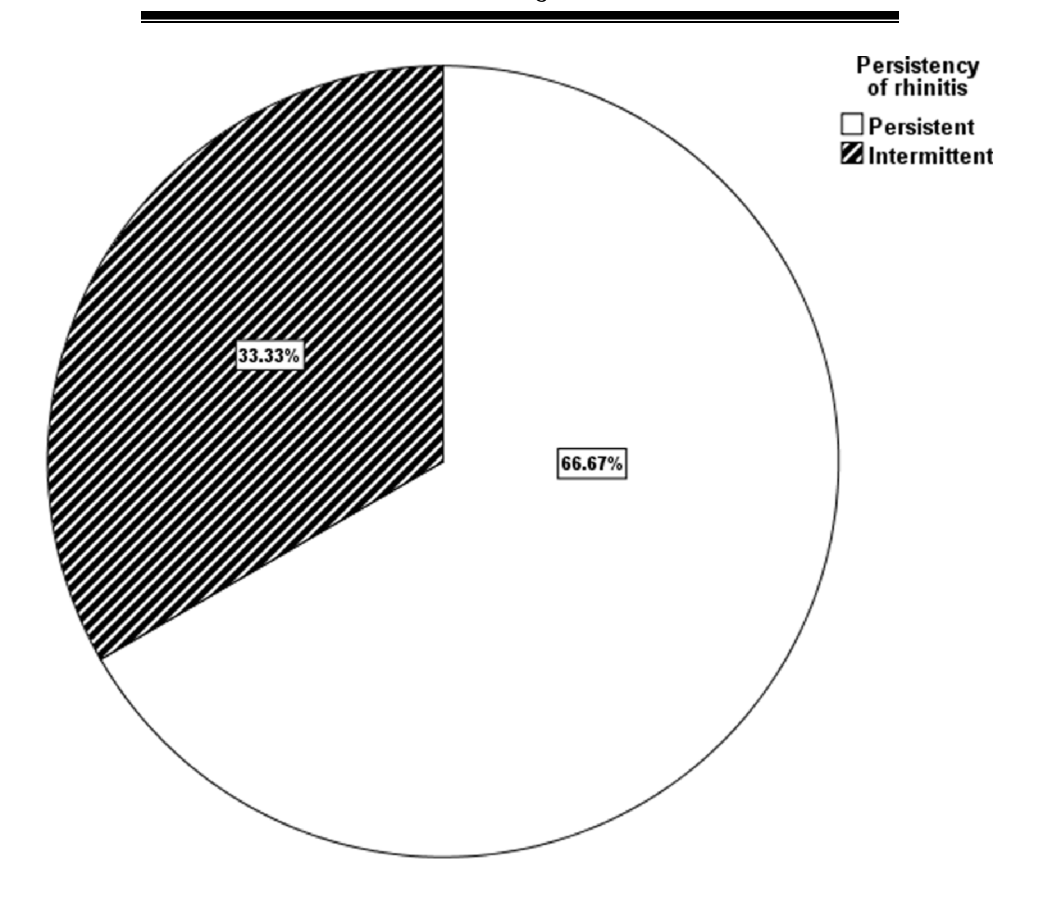


Figure 4. Persistency of rhinitis in the whole study population.

This figure show among whole study population there is 66.67% of them come with persistent symptoms while 33.33% come with intermittent symptoms.

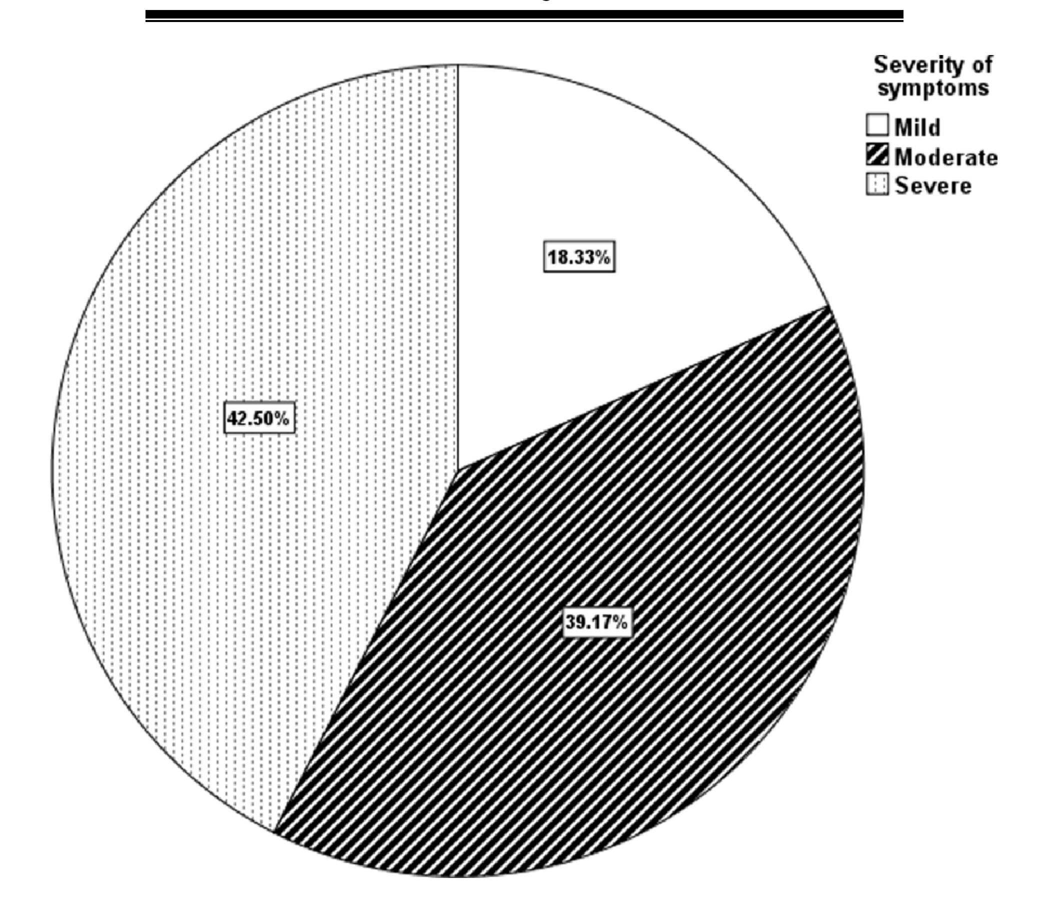


Figure 5. Severity of symptoms in the whole study population.

This figure show Severity of symptoms in the whole study population: 18.33% come with mild symptoms, 39.17% come with moderate symptoms and 42.50% come with sever symptoms.

Table 4. Results of skin prick test and prevalence of high total IgE level in the whole study population

Variable		Number	Percent
Skin prick test	*Positive*	96	80.0
	Negative	24	20.0
Total IgE	*≥100 IU/l*	96	80.0
	<100 IU/l	24	20.0

This table show that there is 96 patient (80%) give a positive skin prick test and positive total serum IgE, while 24 patient (20%) give a negative skin prick test and negative total serum IgE.

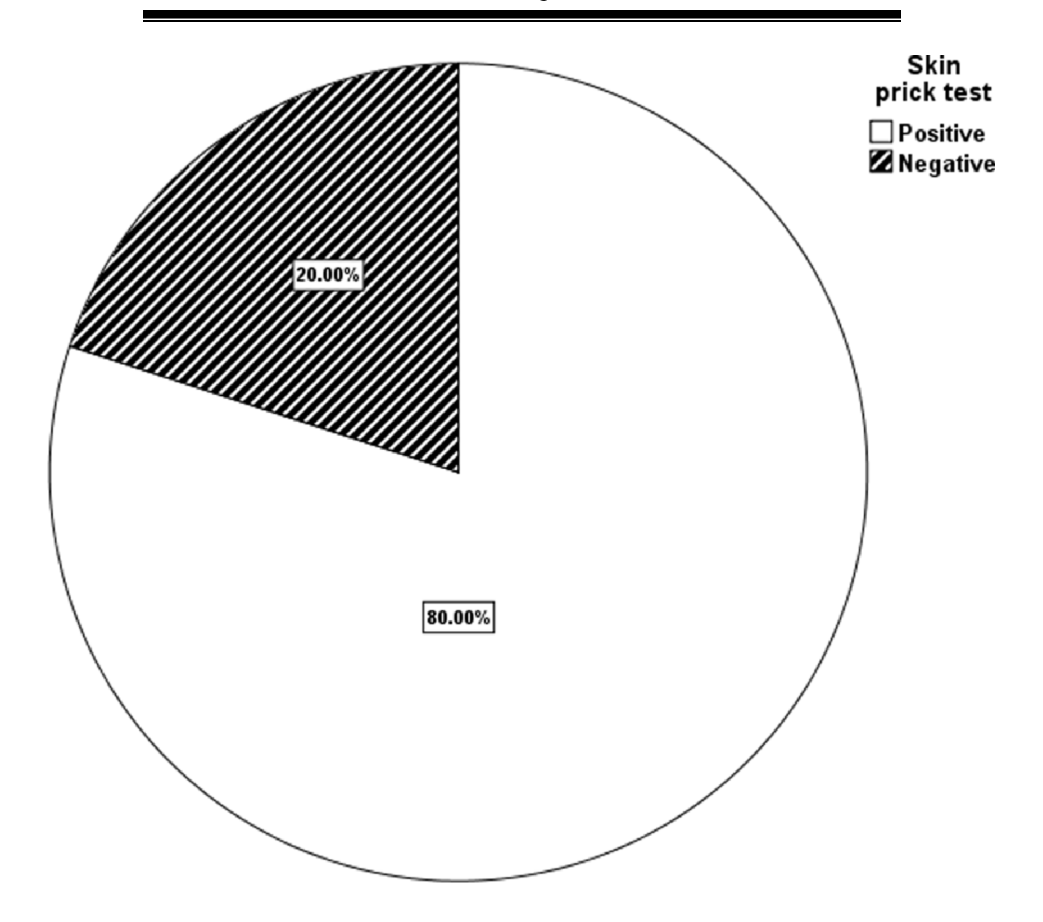


Figure 6. Results of skin prick test in the whole study population.

This figure show that among all patients in our study 80% give positive S.P.T and 20% give negative S.P.T.

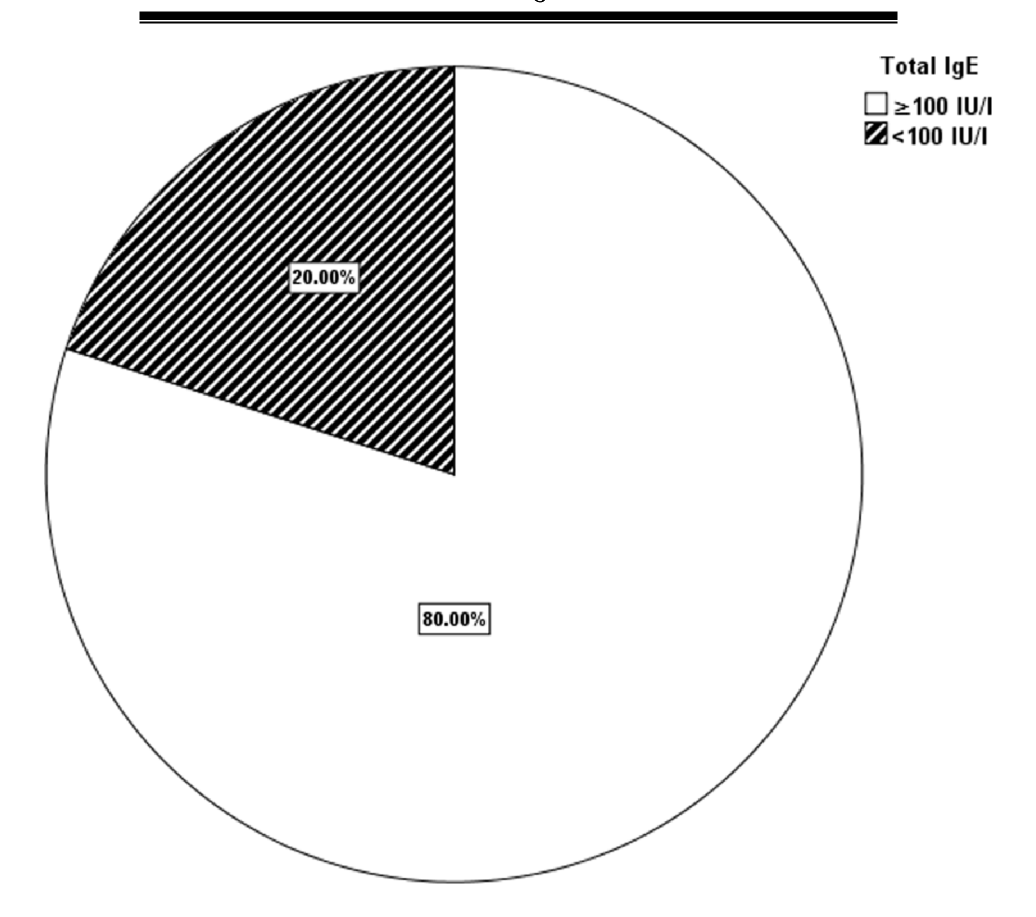


Figure 7. Prevalence of high total IgE level in the whole study population.

Table 5. Total IgE level in the whole study population

Variable	Minimum	Maximum	Mean	SD	Median	IQR
Total IgE (IU/lm)	23.6	1341.3	212.9	204.4	161.0	103.3 - 235.5

SD, standard deviation; IQR, interquartile range.

This table show the level of serum total IgE in whole study population, which range from 23.6 iu/lm to 1341.3 iu/lm with mean 212.9 iu/lm.

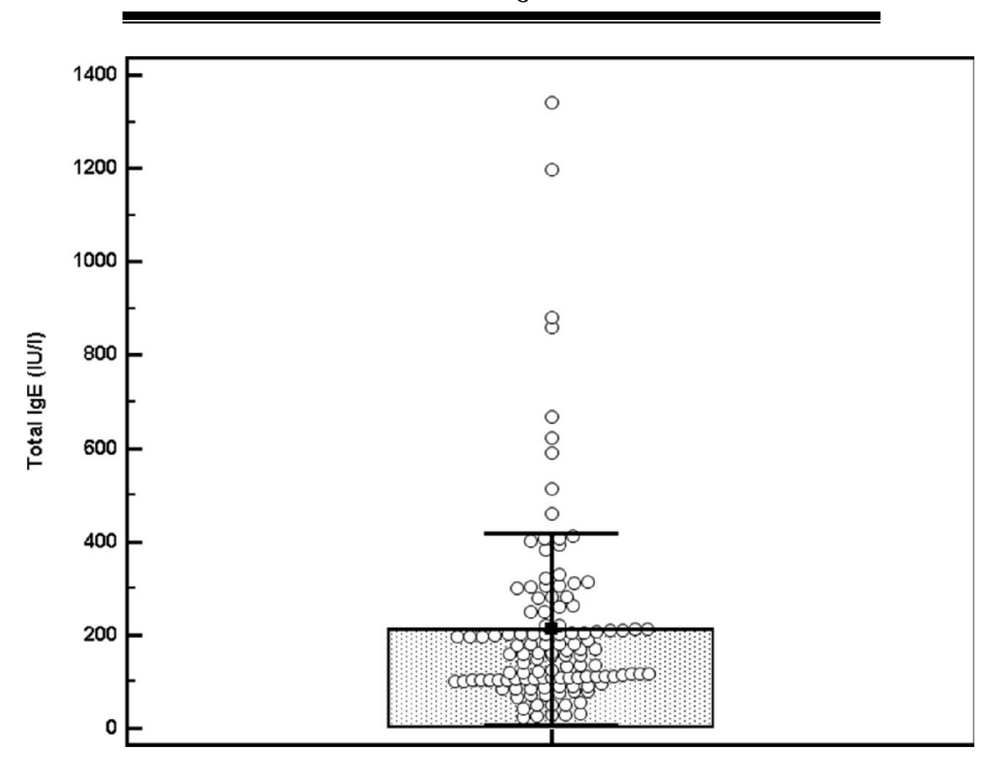


Figure 8. Total IgE level in the whole study population

Table 6. Results of nasal provocation test and prevalence of high nasal-specific IgE level in patients with low total IgE level and negative S.P.T

Variable		Frequency	Percent
Nasal provocation test	*Positive*	15	12.5
	Negative	9	7.5
Nasal-specific IgE	*≥0.350 kU/ml*	10	8.3
	<0.350 kU/ml	14	11.7

This table show that among the 24 patient who give negative skin prick test and low total serum IgE, there is 15 patient (12.5% of whole study patients) give a positive nasal allergen provocation (NAPT) test, and 9 patients (7.5% of whole study patients) give a negative NAPT. And among this 24 patient 10 of them give a positive nasal-specific IgE and 14 give a negative nasal-specific IgE.

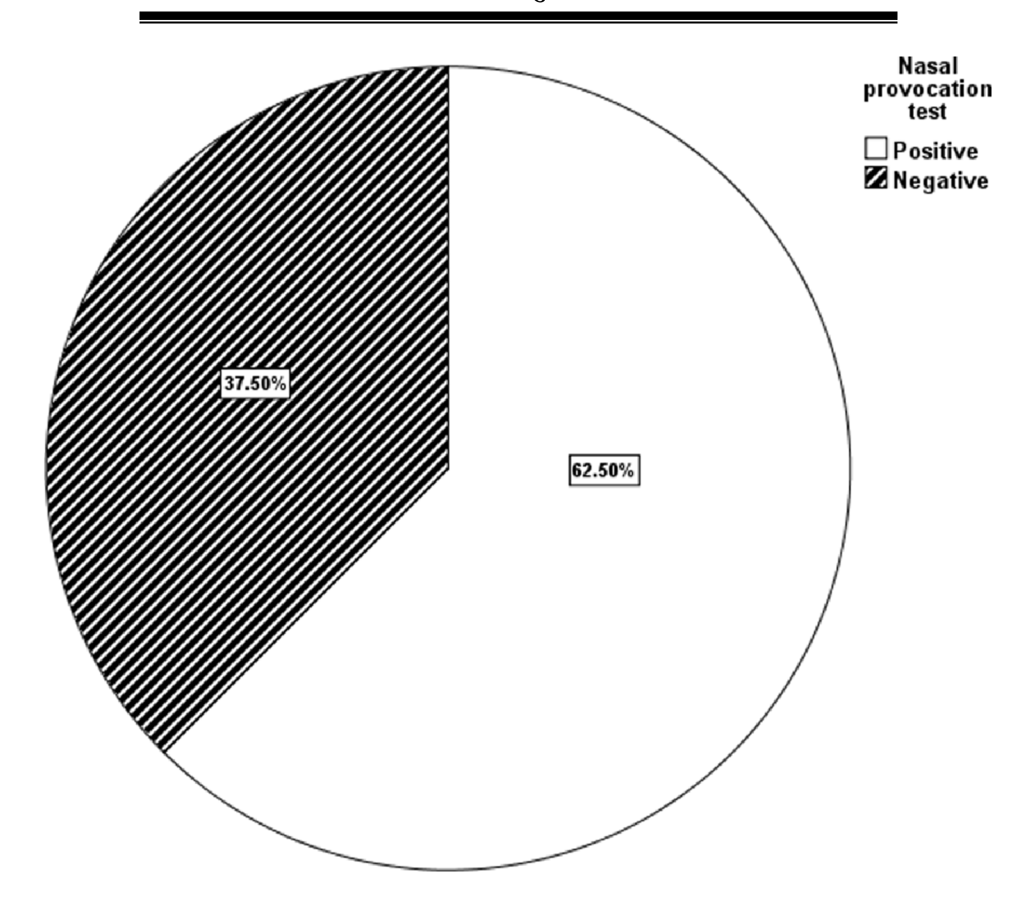


Figure 9. Results of nasal provocation test in patients with low total IgE level and negative S.P.T

In this figure show that among the 24 patient whom give a negative S.P.T and low total serum IgE there is (62.5%) give positive nasal provocation test this group represent local allergic rhinitis (LAR) patients, and (37.5%) give negative nasal provocation test which represent the non-allergic rhinitis patients (NAR).

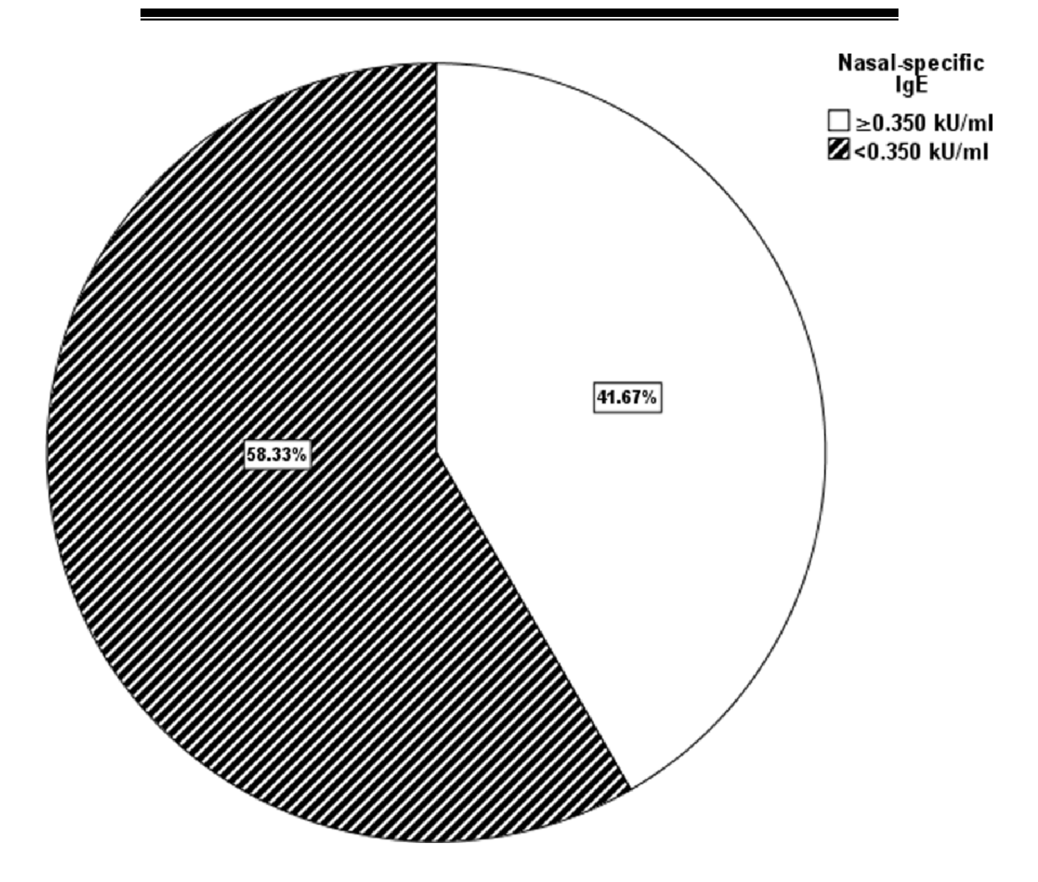


Figure 10. Prevalence of high nasal-specific IgE level in patients with low total IgE level.

This figure show that among 24 patient whom give a negative S.P.T and low total serum IgE there is (41.67%) of them have a detected positive nasal-specific IgE, and (58.33%) of them give a negative detection of nasal-specific IgE.

Table 7. Ultimate diagnosis

		Number	**Percent**
Ultimate diagnosis	*Systemic allergic rhinitis*	96	80.0
	Local allergic rhinitis	15	12.5
	Non-allergic rhinitis	9	7.5

This table show that among the all 120 patient in our study there is 96 patient (80%) give a positive S.P.T and positive serum total IgE which represent the patients with systemic allergic rhinitis (AR). And there is 15 patient (12.5%) give a negative S.P.T, negative total serum IgE and positive nasal allergen provocation test with or without positive nasal-specific IgE which represent the patient with local allergic rhinitis (LAR). And there is 9 patient (7.5%) give a negative of all S.P.T, serum total IgE, nasal allergen provocation test and nasal-specific IgE which represent the patients with non-allergic rhinitis (NAR).

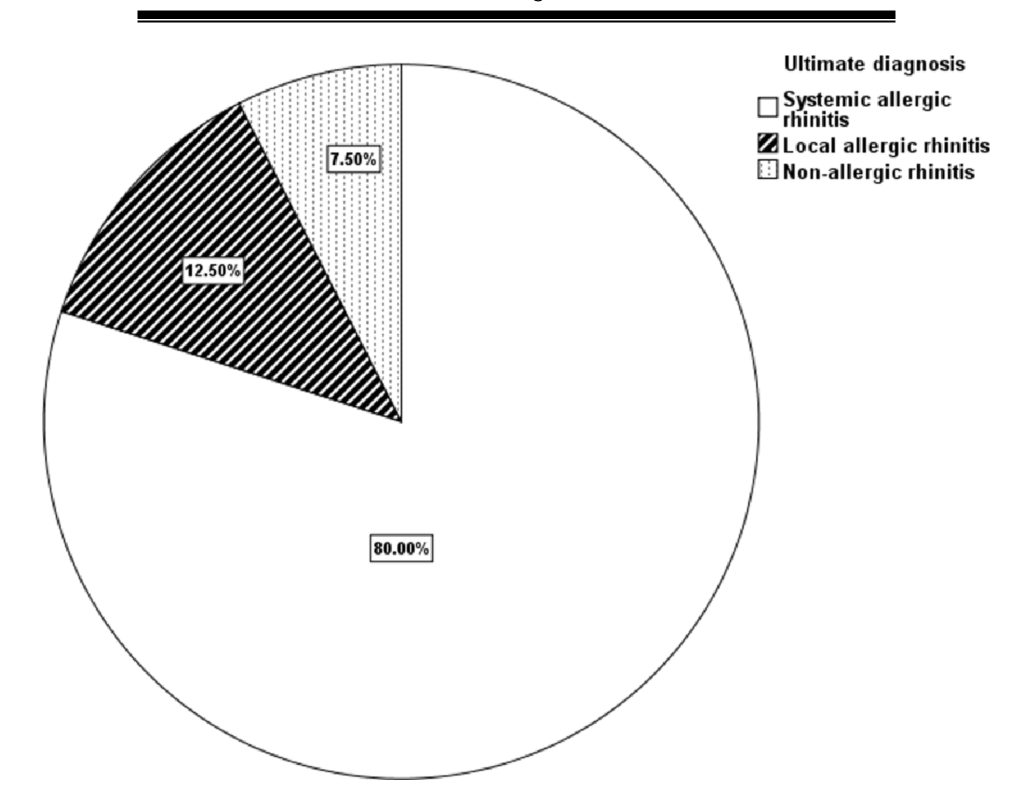


Figure 11. Ultimate diagnosis of rhinitis symptoms.

This figure show among all patients come with symptoms of rhinitis there is 80% of them have system allergic rhinitis (AR) and 12.5% of them have local allergic rhinitis (LAR) and 7.5% of them have non-allergic rhinitis (NAR).

Table 8. Comparison of the three types of rhinitis

Variable	Systemic allergic rhinitis (n=96)	Local allergic rhinitis (n15)	Non-allergic rhinitis (n=9)	p-value
Age (yr)	32 (25 – 40.5)	33 (25.5 – 42)	28 (24 – 35.3)	0.495
Gender				0.360
Male	36 (37.5%)	3 (20.0%)	4 (44.4%)	
Female	60 (62.5%)	12 (80.0%)	5 (55.6%)	
Duration of symptoms (yr)	5 (2.5 – 8)	5 (3.3 – 7.5)	6 (3 – 9.3)	0.513
Persistency of rhinitis				*0.005*
Persistent	65 (67.7%)	13 (86.7%)	2 (22.2%)	
Intermittent	31 (32.3%)	2 (13.3%)	7 (77.8%)	
Severity of symptoms				*0.006*
Mild	17 (17.7%)	1 (6.7%)	4 (44.4%)	
Moderate	37 (38.5%)	5 (33.3%)	5 (55.6%)	
Severe	42 (43.8%)	9 (60.0%)	0 (0.0%)	
Total IgE (IU/l)	193 (121 – 282)†	66 (44.8 – 83)	81 (48.9 – 88)	*<0.001*
Total IgE				*<0.001*
≥100 IU/l	96 (100.0%)	0 (0.0%)	0 (0.0%)	
<100 IU/l	0 (0.0%)	15 (100.0%)	9 (100.0%)	

Data are presented as number (%) or median (interquartile range).

†P<0.001 vs. Local allergic rhinitis & Non-allergic rhinitis groups.

This table show a comparison between the three types of rhinitis in terms of the age, gender, duration of the symptoms, persistency and severity of the symptoms and total serum IgE.

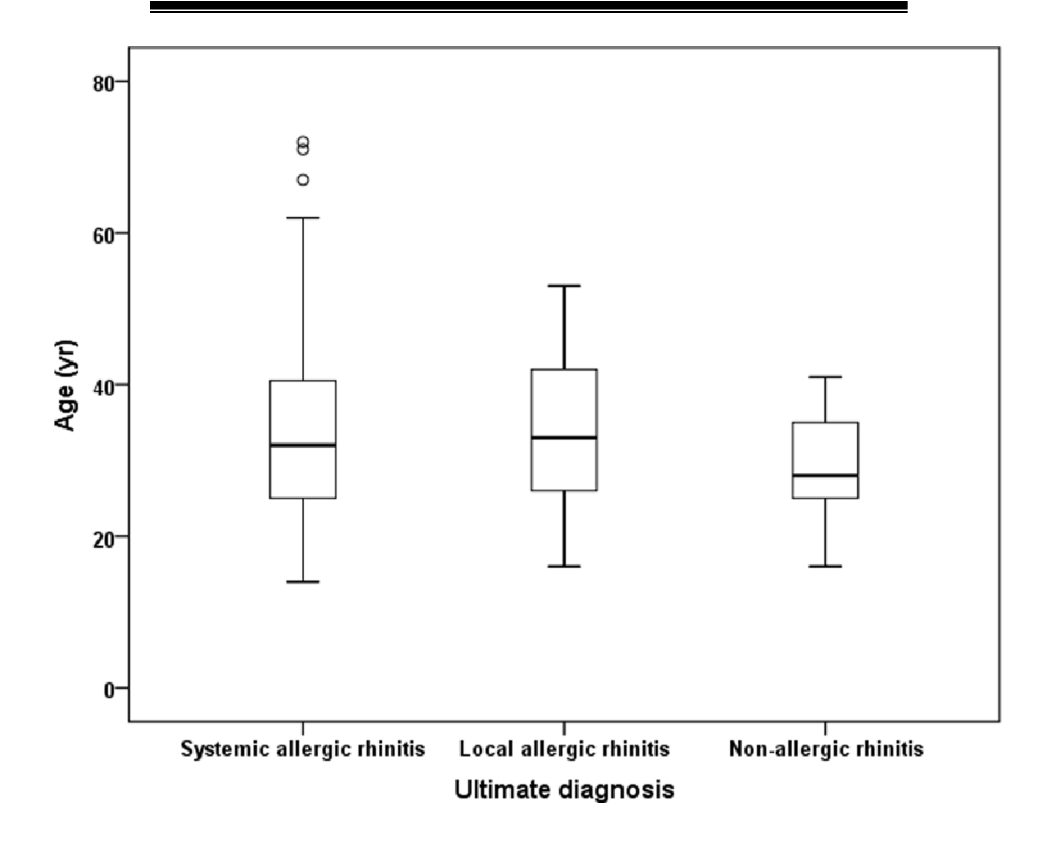


Figure 12. Boxplot showing age in the three forms of rhinitis. Box represents interquartile range. Line across box represents median. Error bars represent minimum and maximum values excluding outliers (rounded markers).

This figure show the age distribution in the three types of rhinitis: most of patients with systemic AR there ages range between (25 – 40.5) with median 32 years old, most patients with LAR there age range between (25.5 - 42) with median 33 years old and most patients with NAR there age range between (24 – 35.3) with median 28 years old.

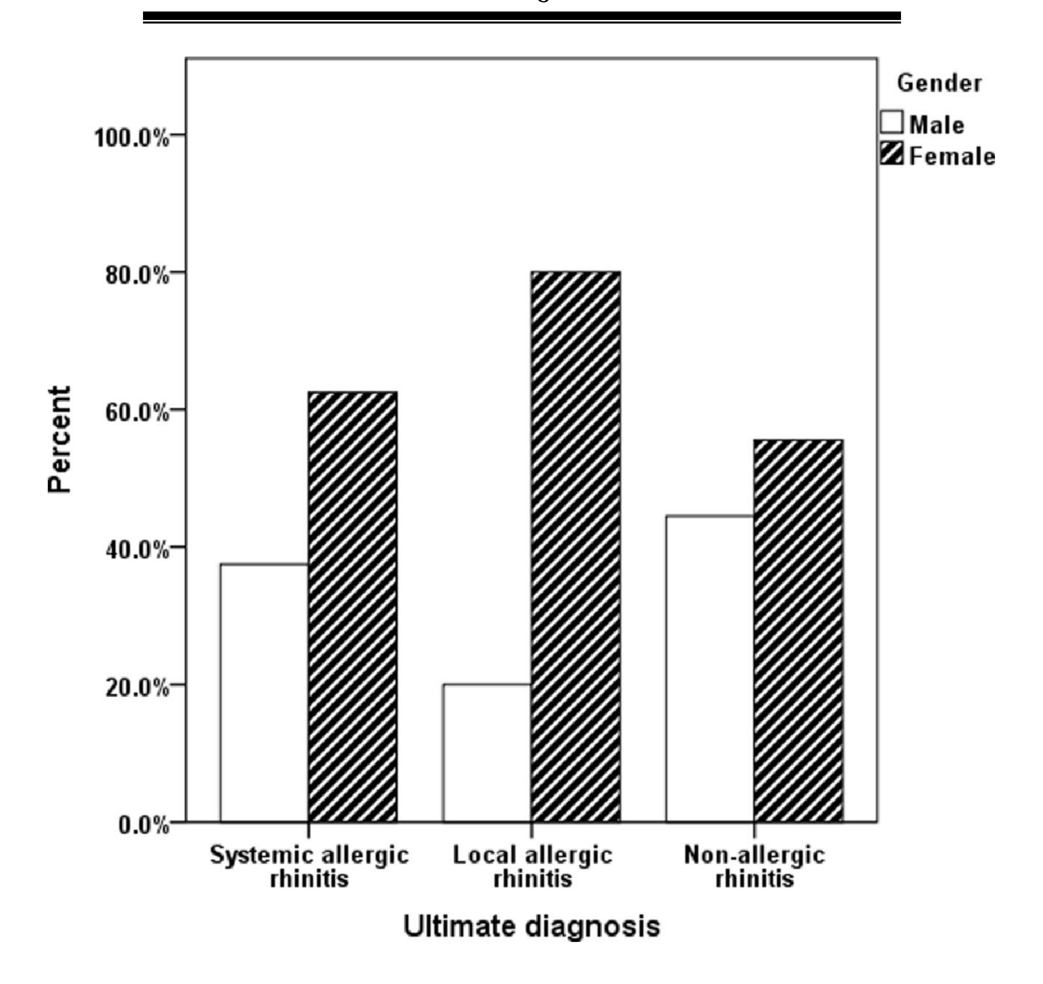


Figure 13. Comparison of gender distribution in the three forms of rhinitis.

This figure show comparison of gender distribution in the three forms of rhinitis: In systemic AR, female patients represent 62.5% and male patients represent 37.5%. In LAR, female patients represent 80% and male patients represent 20%. In NAR, female patients represent 55.6% and male patients represent 44.4%.

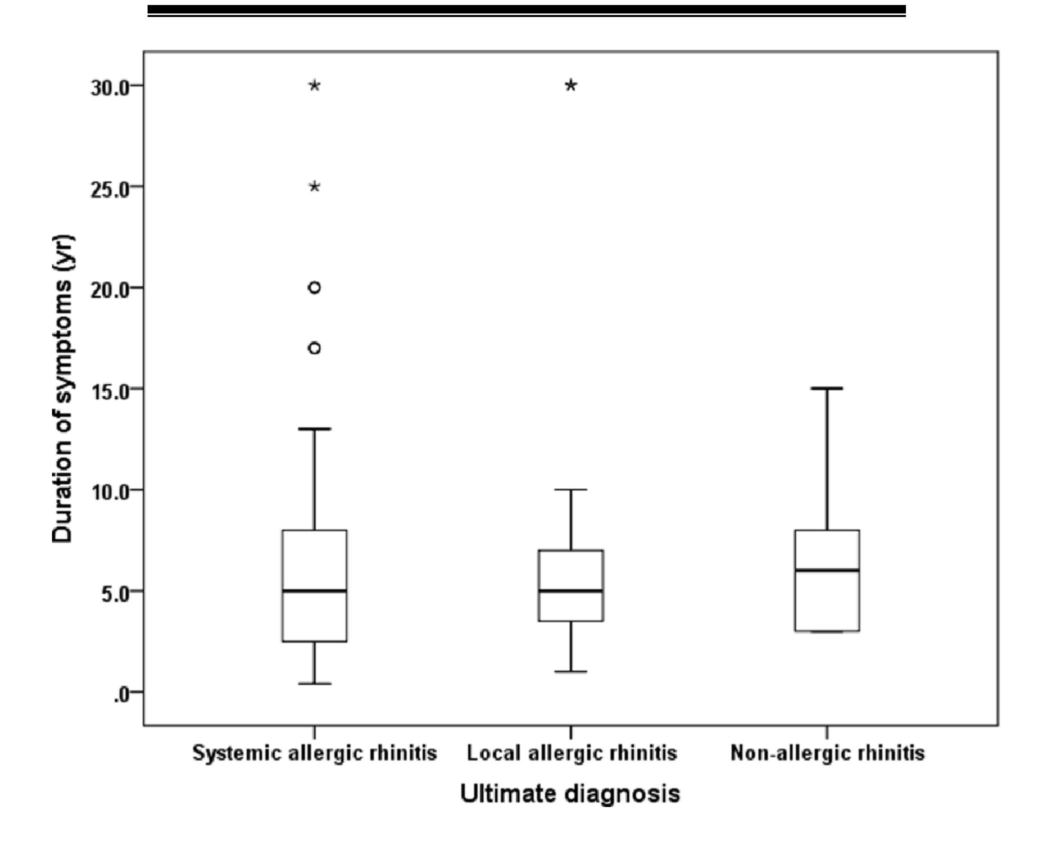


Figure 14. Boxplot showing duration of symptoms in the three forms of rhinitis. Box represents interquartile range. Line across box represents median. Error bars represent minimum and maximum values excluding outliers (rounded markers) and extreme observations (asterisks).

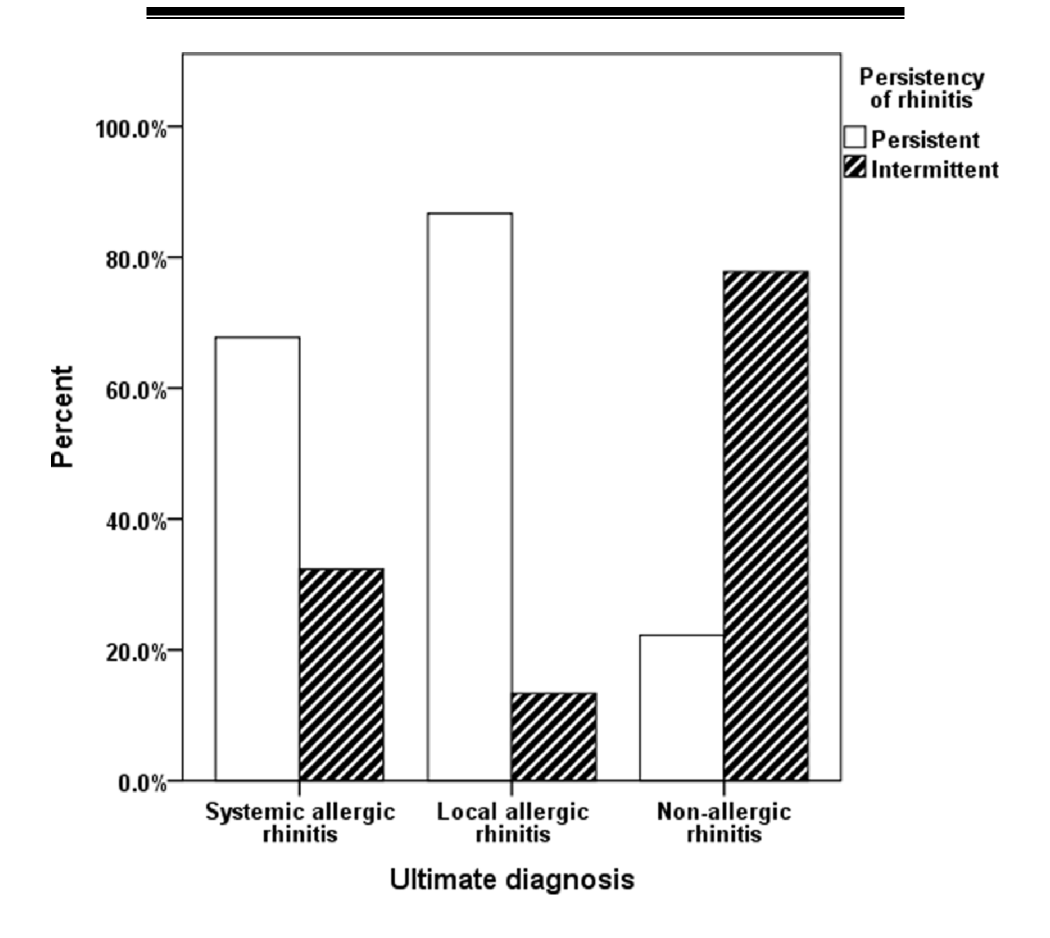


Figure 15. Comparison of the persistency of symptoms in the three forms of rhinitis.

This figure show that in systemic AR, there is 67.7% come with persistent symptoms while 32.3% come with intermittent symptoms. And in LAR, there is 86.7% come with persistent symptoms while 13.3% come with intermittent symptoms. But in NAR, there is 22.2% come with persistent symptoms while 77.8% come with intermittent symptoms.

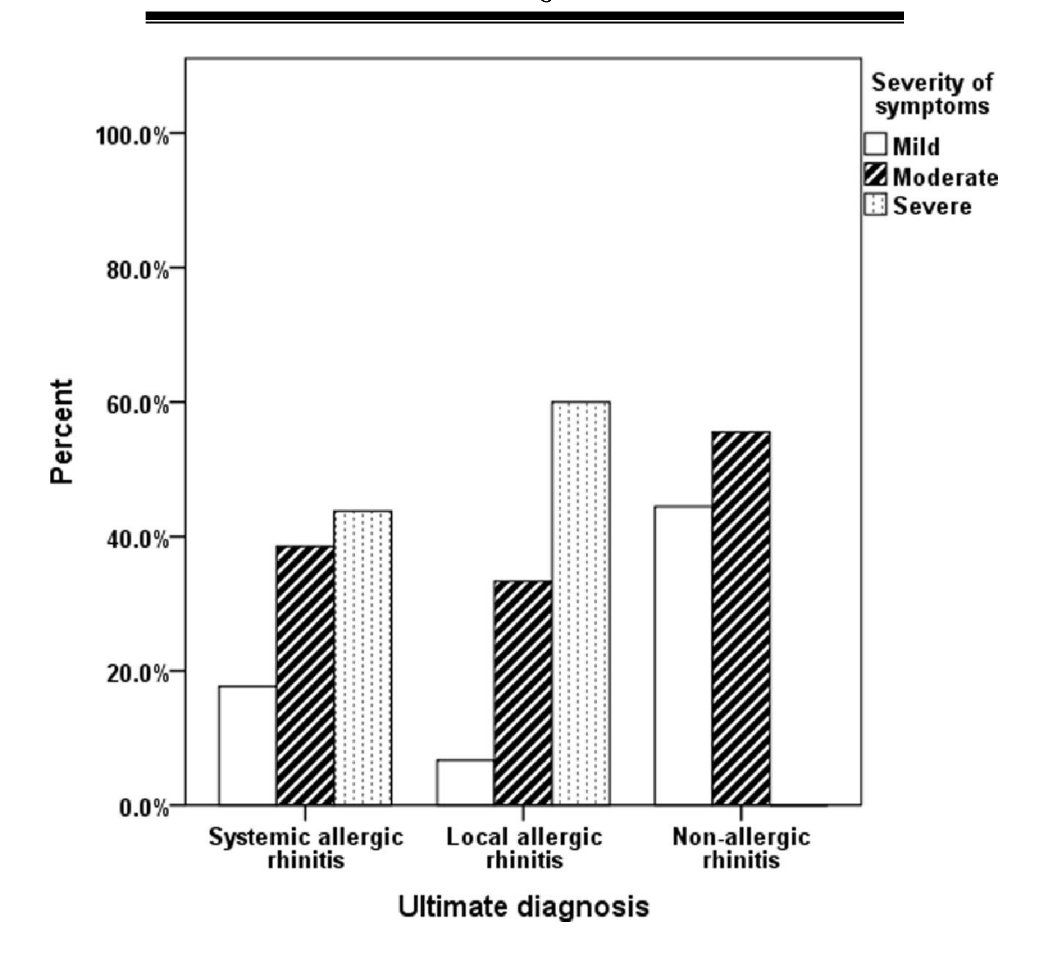


Figure 16. Comparison of the severity of symptoms in the three forms of rhinitis.

This figure show that in systemic AR: there is 17.7% come with mild, 38.5% come with moderate and 43.8% come with sever symptoms. While in LAR there is 6.7% come with mild, 33.3% come with moderate and 60% come with sever symptoms. But in NAR there is 44.4% come with mild and 55.6% come with moderate symptoms.

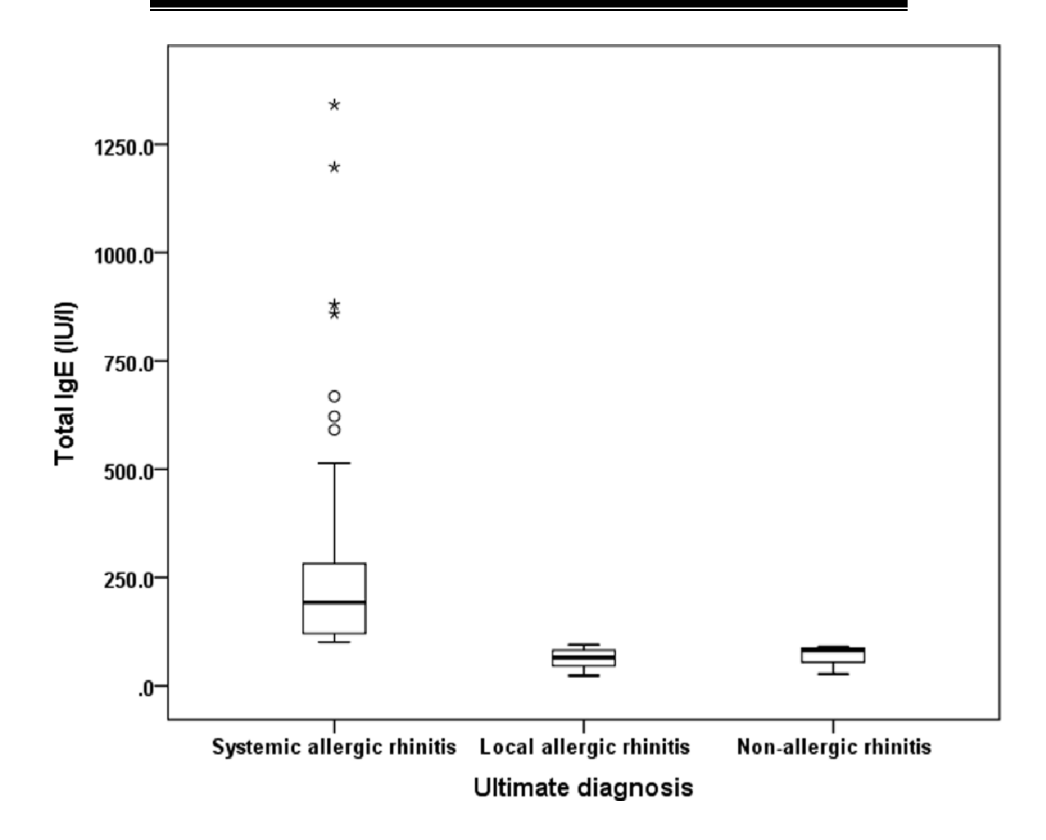


Figure 17. Boxplot showing total IgE level in the three forms of rhinitis. Box represents interquartile range. Line across box represents median. Error bars represent minimum and maximum values excluding outliers (rounded markers) and extreme observations (asterisks).

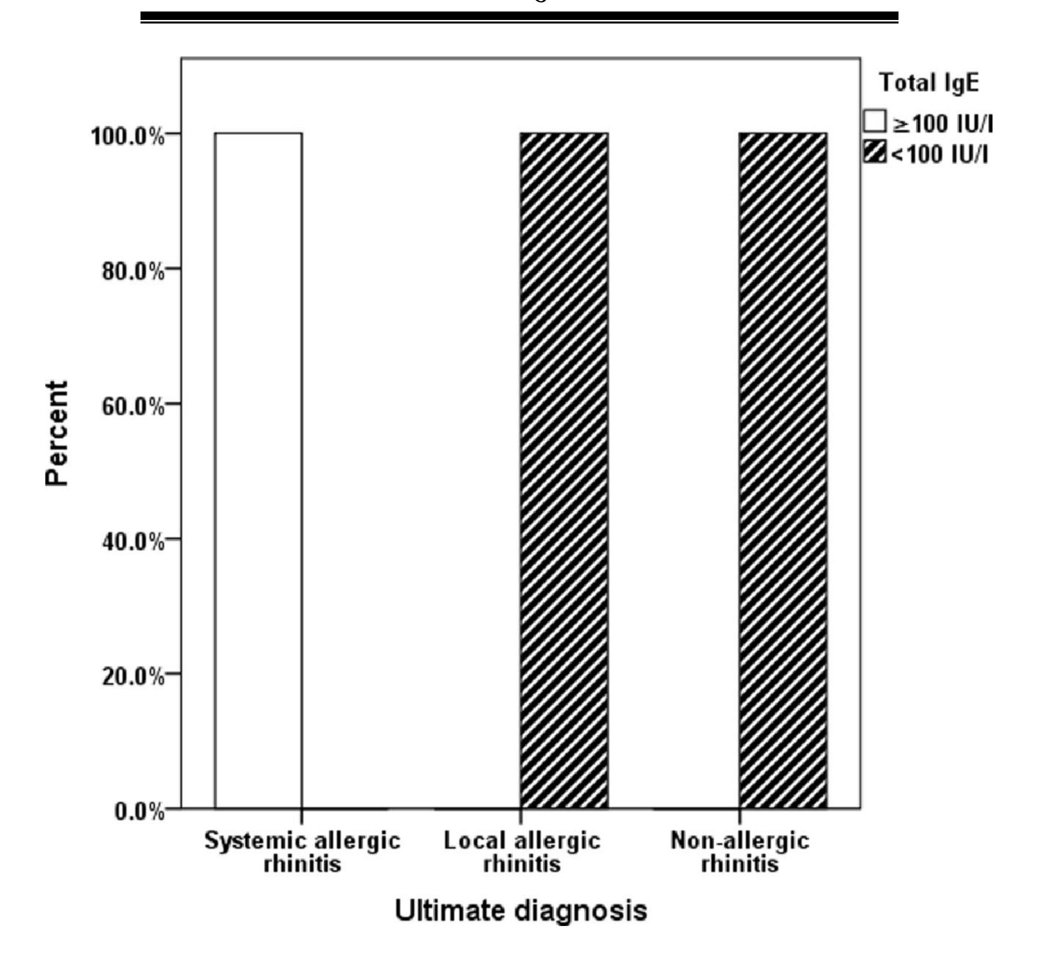


Figure 18. Prevalence of high total IgE level in the three forms of rhinitis.

This figure show that in systemic AR there is a high total serum IgE but in LAR and NAR there is a negative total serum IgE.

Table 9. Value of total IgE for diagnosis of systemic allergic rhinitis

	Systemic allergic rhinitis	Other types of rhinitis	Total
Total IgE ≥100 IU/l	96	0	96
Total IgE <100 IU/l	0	24	24
Total	96	24	120
Sensitivity		100%	
Specificity		100%	
Positive predictive value		100%	
Negative predictive value		100%	
Overall Classification Accuracy		100%	
False Positive Rate (False Alarm)		0%	
False Negative Rate		0%	

This table show the sensitivity and specificity of total serum IgE to determine the systemic AR, which there is a positive serum total IgE among all patient with systemic allergic rhinitis and negative in other types of rhinitis.

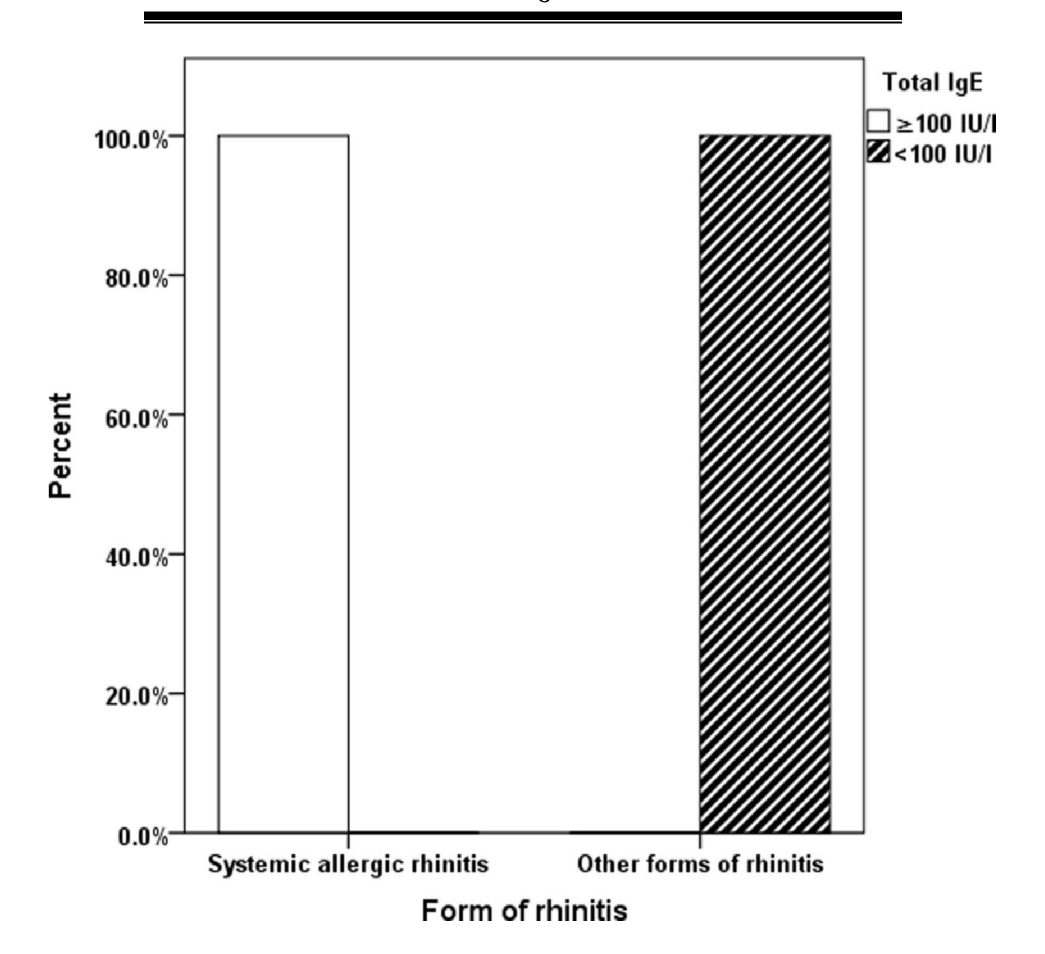


Figure 19. Prevalence of high total IgE level in patients with systemic allergic rhinitis and those with other forms of rhinitis.

Table 10. Value of nasal-specific IgE for diagnosis of local allergic rhinitis

	Local allergic rhinitis	Other types of rhinitis	Total
Nasal-specific IgE ≥0.350 kU/ml	10	0	10
Nasal-specific IgE <0.350 kU/ml	5	9	14
Total	15	9	24
Sensitivity		67%	
Specificity		100%	
Positive predictive value		100%	
Negative predictive value		%64	
Overall Classification Accuracy		%79	
False Positive Rate (False Alarm)		0%	
False Negative Rate		33%	

This table show the sensitivity and specificity of nasal-specific IgE to determine LAR which show among the 15 patients of LAR there is 10 patients have a positive nasal-specific IgE and 5 patients give a negative nasal-specific IgE. While in the 9 patients with NAR all of them give a negative nasal-specific IgE. This give a high specificity (100%) to this test to LAR patients but with low sensitivity (67%).

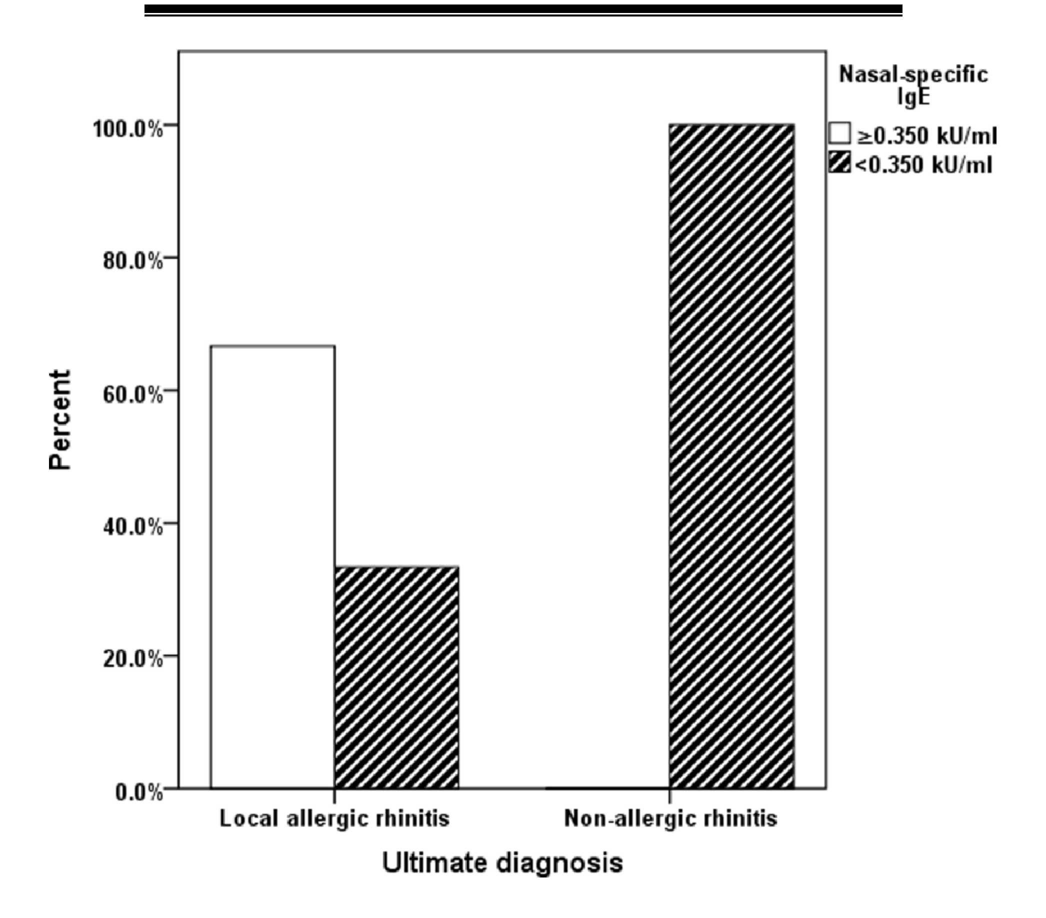


Figure 20. Prevalence of high nasal-specific IgE level in patients with local allergic rhinitis and those with non-allergic rhinitis.

This figure show that in patients with LAR in our study 67% give positive nasal-specific IgE 33% give a negative result. But in patients with NAR in our study all of them give a negative nasal-specific IgE.

Discussion

Idiopathic rhinitis (IR) is an entity that has not been well defined clinically and may have several etiologies and different mechanisms ***(Powe et al, 2001).***

Evidence has demonstrated that some IR patients with symptoms suggestive of allergic rhinitis and a negative skin test and absence of serum IgE antibodies present a new form of local allergic rhinitis 'LAR' or 'entopy' with a local inflammatory response and a local presence of sIgE and a positive response to a NAPT ***(Rondon et al, 2007)***.

In order to identify these patients, a detailed clinical history that excludes subjects with vasomotor or infectious rhinitis is appropriate before initiating pathophysiological studies in LAR or entopy ***(Rondon et al, 2008).***

Although true prevalence data are not available about the local allergic rhinitis phenotype, results generated in various European centers suggest that among patients with negative SPT responses and undetectable IgE antibodies in serum, LAR might be present in 47% to 62.5% of patients with perennial and seasonal symptoms ***(Rondon et al, 2007)***.

Many of these patients were given a diagnosis of IR or NARES previously ***(Carney et al, 2002).*** These data indicate that local allergic

rhinitis (LAR) might be a common, although underestimated entity ***(wedback et al, 2005).***

In our study, conducted on 120 adult Egyptian patients with clinical manifestations suggestive of rhinitis (selected from the allergy outpatient clinic at Ain shams university hospitals between March 2013 to March 2014) show that among all 120 patient on this study, the male gender was 43 patients (35.8%) and female gender was 77 patients (64.2%) with age range between (14 - 72) years old with main age 32.6 years old all of them come with complain of nasal discharges, sneezing, nasal itching or nasal obstruction after exclusion of smoker, pregnant women, on NSAID and patients with chronic rhinosinusitis.

There is only one study done in 2012 by ***Rondon et al*** on the prevalence of local allergic rhinitis in Spain which conducted on 428 randomly selected outpatient over one year complaining of rhinitis symptoms after exclusion of smoker, pregnant women, on NSAID and patients with chronic rhinosinusitis, show female gender was predominant with (62.4%) and male gender was (37.2%) with age ranged (14 - 68) years old ***(Rondon et al, 2012).*** Which are nearly similar to our study results.

In our study, show that among whole 120 conducted patients there is 96 patient (80%) give a positive skin prick test and positive total serum IgE which represent the system allergic rhinitis

patients (AR), and 24 patient (20%) give a negative skin prick test and negative total serum IgE whish represent either local allergic rhinitis (LAR) or non-allergic rhinitis (NAR).

In the study done by ***Rondon et al, 2012*** on 428 conducted patients come with rhinitis on Spain, there is (63.1%) give a positive skin prick test and positive total serum IgE which represent the system allergic rhinitis patients (AR), while (36.9%) give a negative skin prick test and negative total serum IgE whish represent either local allergic rhinitis (LAR) or non-allergic rhinitis (NAR). May be the difference between our study and this study is due to the different of the environmental allergens load and level of allergen exposure in Spain and Europe from Egypt.

In our study, show that among the 24 patient whom give a negative S.P.T and low total serum IgE there is 15 patients (62.5%) give positive nasal allergen provocation test (NAPT) this group represent local allergic rhinitis (LAR) patients, and 9 patients (37.5%) give negative nasal allergen provocation test (NAPT) which represent the non-allergic rhinitis patients (NAR). So that from our study we find that, the prevalence of local allergic rhinitis (LAR) patients among patients come with rhinitis with negative S.P.T and low serum IgE which many of these patients were given a diagnosis of IR or NARES previously is 62.5%.

These results similar to ***Lopez et al*** study, although true prevalence data are not available,

results generated in various European centers suggest that among patients with negative SPT responses and undetectable IgE antibodies in serum، LAR might be present in 47% to 62.5% of patients with perennial and seasonal symptoms. Many of these patients were given a diagnosis of IR or NARES previously ***(Lopez et al, 2008).***

In our study, among 15 patients with local allergic rhinitis (LAR): 10 patients (67%) have a detected positive nasal-specific IgE and 5 patients (33%) haven't a detected nasal-specific IgE in there nasal secretion, while in all patient with non-allergic rhinitis haven't a detected nasal-specific IgE. This show that the nasal-specific IgE test in our study has very high specificity (100%) to local allergic rhinitis patients but with low sensitivity (67%), while nasal allergen provocation test (NAPT) has a high specificity and sensitivity (100%).

In the study done by ***Rondon et al*** diagnosis of LAR can be confirmed based on the detection of nasal sIgE, a positive NAPT response, or both in the absence of systemic atopy. Nasal-specific IgE in vitro test has a high specificity but a low sensitivity of 22% to 40%. Whether the dilution effect of the nasal lavage, a nonspecific response to HDM, other factors, or both, might contribute to this low sensitivity ***(Rondon et al, 2008)***.

And this may explain the difference of the sensitivity of the test (nasal sIgE) in our study which is (67%) from this study which is (22% - 40%) in patients with local allergic rhinitis as we don't do a nasal lavage but take a concentrated nasal secretions not diluted or may due to the difference of the allergen loads, levels and types in Egypt from Europe.

A nasal allergen provocation test with a single aeroallergen (NAPT-S) is a very useful diagnostic tool in patients with LAR with higher sensitivity than determination of nasal sIgE levels ***(Lopez et al, 2010)***.

In our study, we observe that most of patients with allergic rhinitis and those with local allergic rhinitis come with sever persistent symptoms in contrast with patients with non-allergic rhinitis, as in allergic rhinitis patients (67.7%) of them and in local allergic rhinitis (86.7%) of them come with persistent frequency while in non-allergic rhinitis patients only (22.2%) come with persistent frequency. Moreover, in allergic rhinitis patient (43.8%) of them and in local allergic rhinitis (60%) of them come with severe symptoms while in non-allergic rhinitis patients none of them comes with severe symptoms.

The majority of patients with LAR studied reported persistent rhinitis with moderate-to-severe symptoms frequently associated with

conjunctivitis (25% to 57%) and asthma (33% to 47***%) (Rondon et al, 2011).***

In the study done by ***Rondon et al*** there is LAR patients in Spain (90.9%) of them come with persistent frequency, while (59.1%) of them come with severe symptoms and (36.4%) with moderate symptoms.

At the end of our study, we clarified that the prevalence of local allergic rhinitis (LAR) among all 120 patients randomly selected over one year selected from the allergy outpatient clinic at Ain Shams University hospitals come with manifestation of rhinitis was (12.5%) while systemic allergic rhinitis (80%) and non-allergic rhinitis (7.5%).

In the study which represents the first attempt to evaluate the prevalence of LAR in comparison with AR and NAR in a population suffering from nasal symptoms done by ***Rondon et al*** in random sample of 428 new adult rhinitis patients who attended our allergy service over a 1 year period was studied, The prevalence of LAR was (25.7%), AR (63.1%), and NAR (11.2%) **(*Rondon et al, 2012).***

The difference between our study prevalence and ***Rondon et al*** study prevalence may due to their large sample size in compare with our study and the difference of the environment in Europe from Egypt, differ types and level of

allergen exposure and it’s the first study done up till now for evaluation of LAR prevalence so there is no more data available for another places similar to our environment.

Summary

Rhinitis is a global health problem that affects 20%-40% of the population in developed countries and whose incidence is rising. It can be induced by different mechanisms and involves several etiological agents. Rhinitis has traditionally been classified as allergic rhinitis (AR) and nonallergic rhinitis (NAR)

The diagnosis of AR is based on clinical manifestations and supported by a positive result for skin prick test (SPT) or serum immunoglobulin E (IgE) antibodies to aeroallergens. In contrast, rhinitis is diagnosed as nonallergic when an allergic cause has been ruled out by the presence of an inconsistent clinical history, a negative SPT, and the absence of serum IgE antibodies.

Nonallergic rhinitis is a very heterogeneous group of conditions that can be subdivided into several phenotypes, the largest of which are idiopathic rhinitis and nonallergic rhinitis with eosinophilia syndrome (NARES) In recent years, several studies have shown that many patients previously diagnosed with NAR or idiopathic rhinitis (IR) develops local allergic rhinitis (LAR) or entopy.

Local allergic rhinitis (LAR) is a localized nasal allergic response in the absence of systemic atopy characterized by local production of specific

IgE (sIgE) antibodies, a TH2 pattern of mucosal cell infiltration during natural exposure to aeroallergens and a positive nasal allergen provocation test response with release of inflammatory mediators (tryptase and eosinophil cationic protein).

Although true prevalence data are not available, results generated in various European centers suggest that among patients with negative SPT responses and undetectable IgE antibodies in serum، LAR might be present in 47% to 62.5% of patients with perennial and seasonal symptoms. Many of these patients were given a diagnosis of IR or NARES previously. These data indicate that LAR might be a common, although underestimated entity.

This study, conducted on 120 adult Egyptian patients with clinical manifestations suggestive of rhinitis (selected from the allergy outpatient clinic at Ain shams university hospitals between March 2013 to March 2014).

All patients were subjected to full medical history taking, Clinical examination, Skin prick test and Serum total IgE by ELISA. While patients with negative S.P.T and negative total serum IgE were subjected to nasal allergen provocation test (NAPT) by common aeroallergen and nasal specific IgE (sIgE) by ELISA.

We observed from this study:

Show that among whole 120 conducted patients there is 96 patient (80%) give a positive skin prick test and positive total serum IgE which represent the system allergic rhinitis patients (AR), and 24 patient (20%) give a negative skin prick test and negative total serum IgE whish represent either local allergic rhinitis (LAR) or non-allergic rhinitis (NAR).

Among the 24 patient whom give a negative S.P.T and low total serum IgE there is 15 patients (62.5%) give positive nasal allergen provocation test (NAPT) this group represent local allergic rhinitis (LAR) patients, and 9 patients (37.5%) give negative nasal allergen provocation test (NAPT) which represent the non-allergic rhinitis patients (NAR).

So that from our study we find that, the prevalence of local allergic rhinitis (LAR) patients among patients come with rhinitis with negative S.P.T and low serum IgE which many of these patients were given a diagnosis of IR or NARES previously is 62.5%.

Among 15 patients with local allergic rhinitis (LAR): 10 patients (67%) have a detected positive nasal-specific IgE and 5 patients (33%) haven't a detected nasal-specific IgE in there nasal secretion, while in all patient with non-allergic rhinitis haven't a detected nasal-specific IgE.

This show that the nasal-specific IgE test in our study has very high specificity (100%) to local allergic rhinitis patients but with low sensitivity (67%), while nasal allergen provocation test

(NAPT) has a high specificity and sensitivity (100%).

At the end of our study, we clarified that the prevalence of local allergic rhinitis (LAR) among all 120 patients randomly selected over one year selected from the allergy outpatient clinic at Ain Shams University hospitals come with manifestation of rhinitis was (12.5%) while systemic allergic rhinitis (80%) and non-allergic rhinitis (7.5%).

Recommendations

A significant research effort with large number of patients will be required over the coming years in more countries to address all of the following questions:

- What are the prevalence and overall effect of LAR, and what is the influence of environmental factors on the epidemiology of this condition?
- Are the allergens associated with LAR the same as those involved in conventional AR?
- How definitive is the evidence that IgE is produced locally in the nasal mucosa?
- Is IgE production limited to the nose and why?
- Is LAR a precursor or an end stage of systemic atopy, or does it represent a distinct entity with an independent natural history?
- Is optimal LAR management identical to that of conventional AR?